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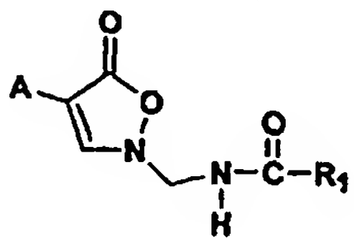

(I)

(57) Abstract

This invention describes isoxazolinone derivatives which possess antibacterial activity and are useful in the treatment of bacterial diseases. More particularly, new isoxazolinones are provided having general formula (I), wherein A and R_1 are as described in the specification.

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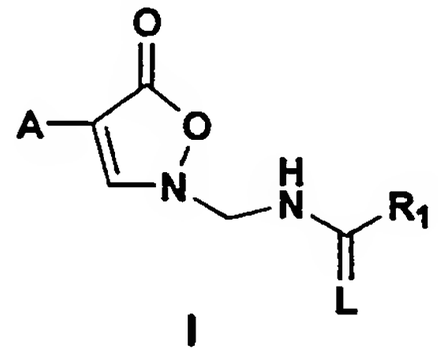
NOVEL ISOXAZOLINONE ANTIBACTERIAL AGENTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed toward new isoxazolinones, methods for their use, and processes for their production. The present invention provides for a compound represented by the general formula



I

or a pharmaceutically acceptable salt thereof wherein:

R_1 is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, or C_{1-8} acyloxy,

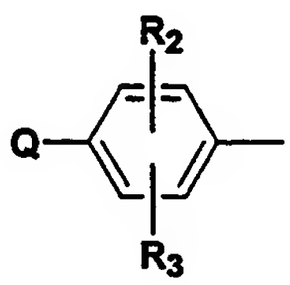
c) C_{3-6} cycloalkyl, or

d) C_{1-8} alkoxy;

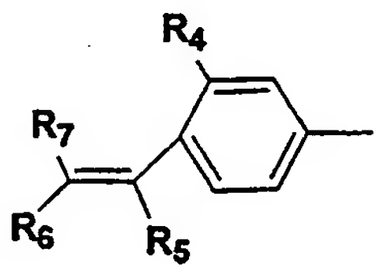
L is oxygen or sulfur;

A is

a)



b)

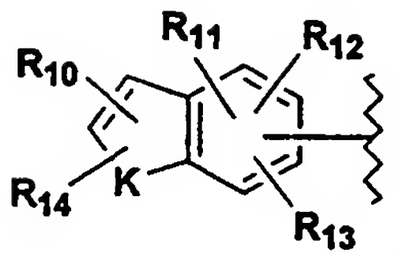


c) a 5-membered heteroaromatic moiety having one to three hetero atoms selected from the group consisting of S, N, and O, wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom and can additionally have a fused-on benzene or naphthyl ring, and wherein the heteroaromatic moiety is optionally substituted with one to three R_8,

d) a 6-membered heteroaromatic moiety having at least one nitrogen atom, wherein the heteroaromatic moiety is bonded via a carbon atom, wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three R_9,

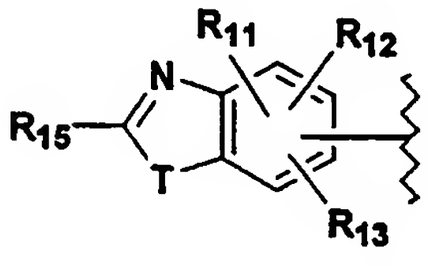
e) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_9,

f)



, or

g)



;

wherein R_2 and R_3 are each independently

a) H,

b) F,

c) Cl,

d) Br,

e) C_{1-6} alkyl,

f) NO_2,

g) I,

h) C_{1-6} alkoxy,

i) OH

j) amino,

k) cyano, or

l) R_2 and R_3 taken together are $-O(CH_2)_h-O$;

wherein R_4 is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_5 is

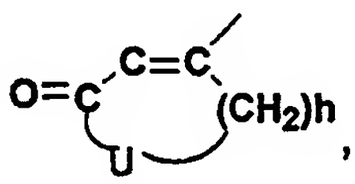
a) H,

b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_5 and R_6 taken together are a 5-, 6-, or 7-membered ring of the formula,



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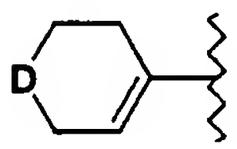
f)



in which D is S, O or NR_{86} in which R_{86} is H or C_{1-6} alkyl, or

g) R_5 and R_6 taken together are $-(CH_2)_k-$, when R_7 is an electron-withdrawing group;

R_6 and R_7 at each occurrence are the same or different and are

a) an electron-withdrawing group,

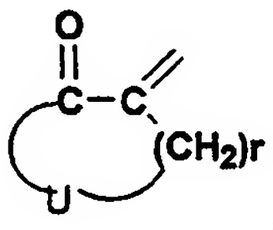
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_6 and R_7 is an electron-withdrawing group, or

f) R_6 and R_7 taken together are a 5-, 6-, or 7-membered ring of the formula,



;

U is

a) CH_2,

b) O,

c) S or,

d) NR_{16};

R_{16} is

a) H or

b) C_{1-5} alkyl;

wherein R_8 is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

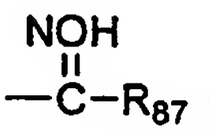
h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) $-NR_{17}R_{18}$,

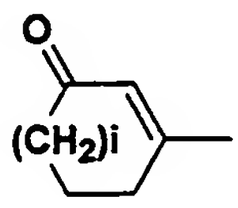
m)  in which R_{87} is H or C_{1-6} alkyl,

n) C_{1-6} alkyl optionally substituted with OH, sulfamoyl, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{17}R_{18}$,

o) C_{2-8} alkyl optionally substituted with one or two R_{19},

p) phenyl optionally substituted with one or two R_{19},

q) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{19}, or



;

R_{17} and R_{18} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) C_{5-6} cycloalkyl, or

d) R_{17} and R_{18} taken together with the nitrogen atom is a 5- or 6-membered saturated or unsaturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, formyl, a 5- or 6-membered heteroaromatic moiety containing 1-3 O, N or S, $-\overset{O}{\overset{\|}{C}}-NR_{88}R_{89}$ in which R_{88} and R_{89} are each independently hydrogen or C_{1-6} alkyl, SO_2R_{90} in which R_{90} is H or C_{1-6} alkyl, or C_{1-3} acyl optionally substituted with 1 or more F, Cl or OH;

R_{19} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{17}R_{18}$,

m) phenyl,

n) $-C(=O)NR_{20}R_{21}$,

o) $-N\ R_{17}R_{18}$,

p) $-N(R_{20})(-SO_2R_{22})$,

q) $-SO_2-NR_{20}R_{21}$, or

r) $-S(=O)_iR_{22}$;

R_{20} and R_{21} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl, or

c) phenyl;

R_{22} is

a) C_{1-4} alkyl, or

b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_9 is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) $-NR_{23}R_{24}$,

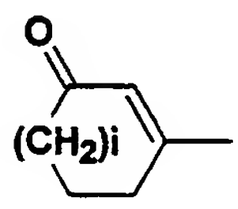
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{23}R_{24}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{25},

o) phenyl optionally substituted with one or two R_{25},

p) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{25}, or

q)



,

R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{23} and R_{24} taken together with the nitrogen atom is a 5- or 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{25} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

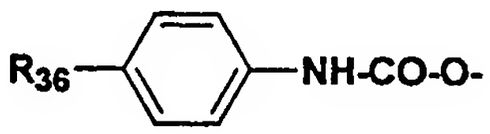
i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{32}R_{33}$, $-SR_{34}$, $-O-SO_2R_{35}$, or



n) $-C(=O)NR_{26}R_{27}$,

o) $-NR_{23}R_{24}$,

p) $-N(R_{26})(-SO_2R_{22})$,

q) $-SO_2-NR_{26}R_{27}$, or

r) $-S(=O)_iR_{22}$,

s) $-CH=N-R_{28}$, or

t) $-CH(OH)-SO_3R_{31}$;

R_{22} is the same as defined above;

R_{26} and R_{27} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{28} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{29}R_{30}$;

R_{29} and R_{30} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{31} is

a) H, or

b) a sodium ion;

R_{32} and R_{33} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

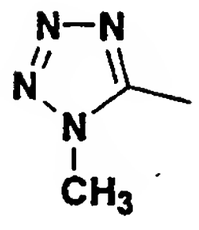
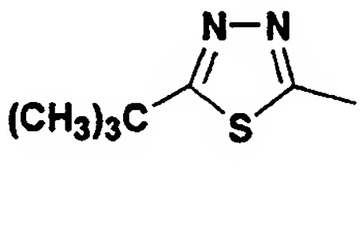
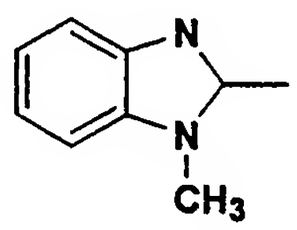
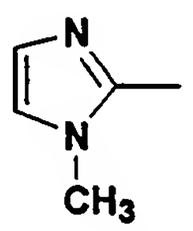
f) C_{3-6} cycloalkyl,

g) R_{32} and R_{33} taken together are a 5- or 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{37})(OR_{38})$, or

i) $-SO_2-R_{39}$;

R_{34} is

R_{35} is C_{1-3} alkyl;

R_{36} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{37} and R_{38} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{39} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O,

b) S, or

c) NR_{40} in which R_{40} is hydrogen, formyl, C_{1-4} alkyl, C_{1-4} acyl, phenyl, C_{3-6} cycloalkyl, $-P(O)(OR_{37})(OR_{38})$ or $-SO_2-R_{39}$ in which R_{37}, R_{38} and R_{39} are as defined above;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} at each occurrence are the same or different and are

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substitutents (e) and (f) can be optionally substituted with OH, halo, C_{1-6} alkoxyl, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

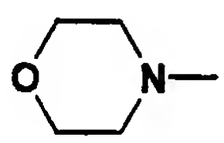
h) $-NR_{42}R_{43}$,

i) OR_{44},

j) $-S(=O)_i-R_{45}$,

k) $-SO_2-N(R_{46})(R_{47})$, or

l) a radical of the following formulas: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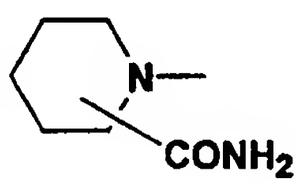
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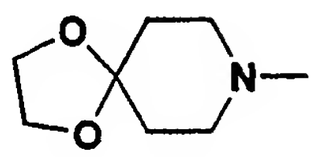
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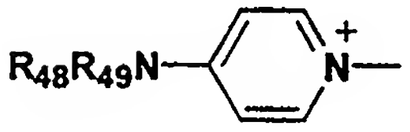
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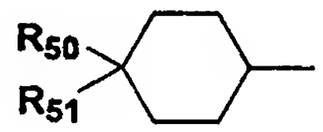
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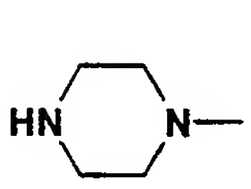
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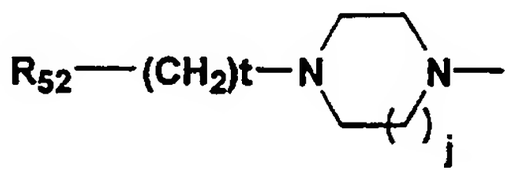
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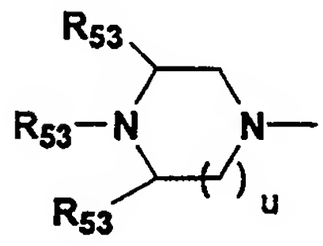

;

R_{19} is the same as defined above;

T is

a) O,

b) S, or

c) SO_2;

R_{42} and R_{43} at each occurrence are the same or different and are

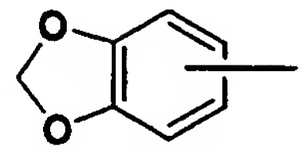
a) H,

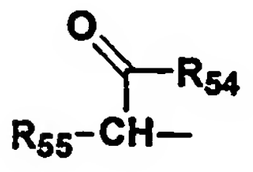
b) C_{3-6} cycloalkyl,

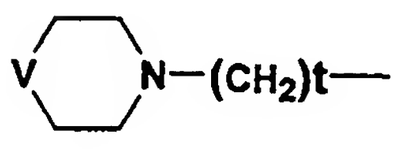
c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5- or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally

substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy,$-NR_{48}R_{49}$, or  ,

f)  , or

g)  ;

V is

a) O,

b) CH_2, or

c) NR_{56};

R_{48} and R_{49} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{54} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{57}R_{58}$;

R_{55} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{56} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{57} and R_{58} at each occurrence are the same or different and are

a) H,

b) C_{1-5} alkyl,

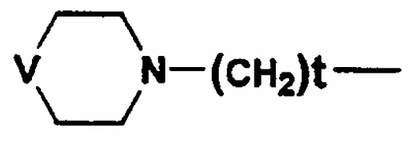
c) C_{1-3} cycloalkyl, or

d) phenyl;

R_{44} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

b)



,

c) phenyl, or

d) pyridyl;

R_{45} is

a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$,

C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{46} and R_{47} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{50} and R_{51} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{48}R_{49}$ in which $R_{48}$and R_{49} are as defined above,

d) R_{50} and R_{51} taken together are =O;

R_{52} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5- or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, wherein the substituents (a) and (b) can in turn be optionally substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

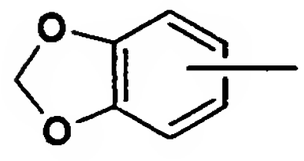
d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{48}R_{49}$ in which $R_{48}$and R_{49} are as defined above,

g) $-C(=O)-R_{59}$, or

h)



;

R_{53} is

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

g) $-P(O)(OR_{37})(OR_{38})$, or

h) $-SO_2R_{39}$, in which R_{37}, R_{38} and R_{39} are as defined above;

R_{59} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0, or 1;

k is 3, 4, or 5;

r is 1, 2, 3, 4, 5 or 6;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2; and

Q is

a) hydrogen,

b) halo,

c) NO_2,

d) N_3,

e) C_1-C_6 alkylthio,

f) C_1-C_6 alkyl—$\overset{O}{\overset{\|}{S}}$—,

g) C_1-C_6 alkyl—$\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}$—,

h) C_1-C_6 alkyl,

i) C_1-C_6 alkoxy,

j) formyl,

k) C_1-C_6 alkyl—$\overset{\overset{O}{\|}}{C}$—,

l) C_1-C_6 alkyl—O-$\overset{\overset{O}{\|}}{C}$—,

m) -sulfamoyl (H_2NSO_2-),

n) -NHOH,

o) C_1-C_6 alkyl—$\overset{\overset{O}{\|}}{C}$-O—,

p) heteroaryl —$\overset{\overset{O}{\|}}{C}$— in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

q) C_6H_5-$\overset{\overset{O}{\|}}{C}$—,

r) amino,

s) C_1-C_6 alkylamino-,

t) di (C_1-C_6 alkyl)amino-,

u) (C_1-C_6) alkyl—$\overset{\overset{O}{\|}}{C}$-$NR_{60}R_{61}$ in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

v) OH,

w) cyano,

x) hydroxy (C_1-C_6 alkyl),

y) C_1-C_6 alkyl—S-$\overset{\overset{O}{\|}}{C}$—,

z) $NC-(CH_2)_r-\overset{O}{\overset{\|}{C}}-$ in which r is 1-6,

aa) $C_6H_5CH_2-O-\overset{O}{\overset{\|}{C}}-$,

bb) $C_6H_5-O-\overset{O}{\overset{\|}{C}}-$,

cc) C_1-C_6 alkyl$-\overset{N-OR_{84}}{\overset{\|}{C}}-$ in which R_{84} is hydrogen or C_{1-6} alkyl,

dd) $R_{85}O-(CH_2)_{1-6}-\overset{O}{\overset{\|}{C}}-$ in which R_{85} is hydrogen, C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy or C_{1-8} acyloxy, C_{3-6} cycloalkyl or C_{1-8} alkoxy;

ee) $H-\overset{N-OR_{84}}{\overset{\|}{C}}-$ in which R_{84} is hydrogen or C_{1-6} alkyl,

ff) a substituted or unsubstituted C_6-C_{10} aryl moiety,

gg) a substituted or unsubstituted monocyclic or bicyclic, saturated or unsaturated, heterocyclic moiety having 1-3 atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent,

hh) a monocyclic or bicyclic substituted or unsubstituted heteroaromatic moiety having 1-3 hetero atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent and wherein the heteroaromatic moiety can additionally have a fused-on benzene or naphthalene ring;

the substituents for such p, q, ff, gg and hh moieties being selected from 1 or 2 of the following:

1) halo,

2) C_{1-6} alkyl,

3) NO_2,

4) N_3,

5) C_1-C_6 alkyl $-\overset{\overset{O}{\|}}{S}-$,

6) C_1-C_6 alkyl $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$,

7) formyl,

8) C_1-C_6 alkyl $-\overset{\overset{O}{\|}}{C}-$,

9) C_1-C_6 alkyl $-O-\overset{\overset{O}{\|}}{C}-$,

10) heteroaryl $-\overset{\overset{O}{\|}}{C}-$ in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

11) $C_6H_5-\overset{\overset{O}{\|}}{C}-$,

12) -(C_1-C_6) alkyl $-\overset{\overset{O}{\|}}{C}-NR_{60}R_{61}$ in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

13) OH,

14) hydroxy (C_1-C_6 alkyl),

15) C_1-C_6 alkyl $-S-\overset{\overset{O}{\|}}{C}-$,

16) $NC-(CH_2)_r-O-\overset{\overset{O}{\|}}{C}-$ in which r is 1-6,

17) $C_6H_5CH_2-O-\overset{\overset{O}{\|}}{C}-$,

18) $-CH_2-R_{80}$ in which R_{80} is

a) $-OR_{32}$ in which R_{32} is as defined above,

b) $-SR_{32}$ in which R_{32} is as defined above,

c) $-NR_{32}R_{33}$ in which R_{32} and R_{33} are as defined above, or

d) 5- or 6-membered heteroaromatic containing 1-4 O, S or N atoms,

19) C_1-C_6 alkyl—C(=N-OR_{84})— in which R_{84} is as defined above,

20) cyano,

21) carboxyl,

22) CF_3,

23) C_1-C_6 alkyl—C(=O)-O—

24) C_6H_5-O-C(=O)— in which the phenyl moiety may be optionally substituted by halo or (C_1-C_6)alkyl,

25) $NR_{60}R_{61}$—C(=O)— in which R_{60} and R_{61} are as defined above,

26) R_{91}-NH-C(=O)— or R_{91}-C(=O)-NH— in which R_{91} is a 5- or 6-membered aromatic heterocyclic group having 1-3 O, N or S,

27) $C_6H_5(CH_2)_{1\text{-}6}$—O-C(=O)—,

28) $R_{85}O$-$(CH_2)_{1\text{-}6}$—O-C(=O)— in which R_{85} is as defined above,

29) $SiR_{99}R_{100}R_{101}$—O-CH_2—C(=O)— in which R_{99}, R_{100} and R_{101} are each independently $C_{1\text{-}6}$ alkyl; or

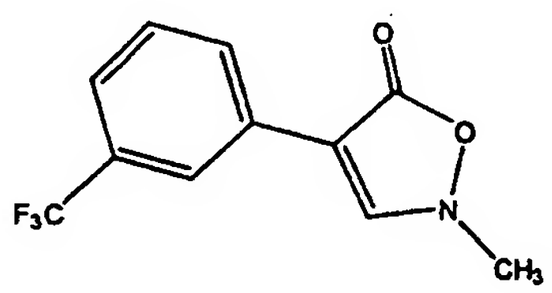
Q and either R_1 and R_2 taken together form –O-CH_2-O.

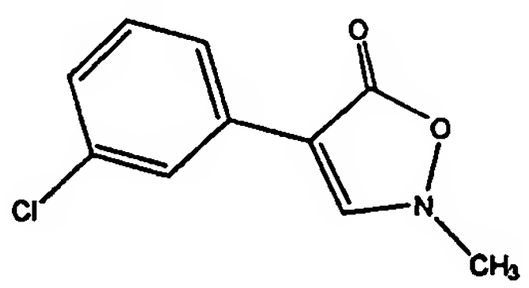
These derivatives are useful as antimicrobial agents which are effective against a number of human and veterinary pathogens, including gram positive bacteria such as multiply-resistant staphylococci,

streptococci, and enterococci, such as methicillin-resistant Staphylococcus aureus or vancomycin-resistant Enterococcus faecium.

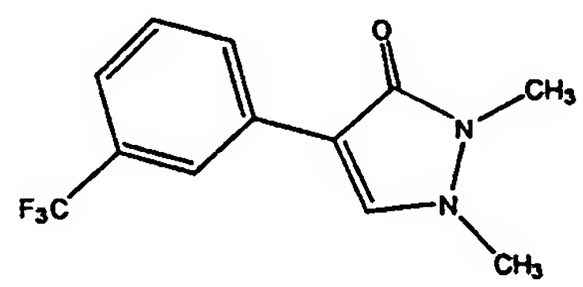
2. Description of the Prior Art

The literature contains a limited number of isoxazolinones used as pre-emergence herbicides. For example in U.S. Patent 4,065,463, 2-methyl-4-(trifluoromethyl-*m*-tolyl)-3-isoxazolin-5-one and 2-methyl-4-(chloro-*m*-tolyl)-3-isoxazolin-5-one are disclosed as being useful in preventing the growth of weeds which have a deleterious effect on crop production.

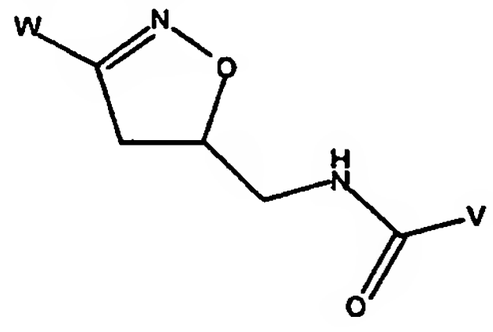




U.S. Patent 4,000,155 discloses the related compound 1,2-dimethyl-4-(trifluoromethyl-*m*-tolyl)-3-pyrazolin-5-one for the same utility.

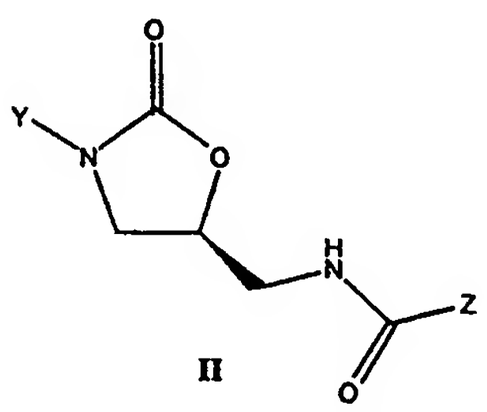


The applicant is not aware of any literature which discloses the use of these compounds as broad spectrum anti-bacterial agents. A different ring system is disclosed in WO 98/07708, which discusses the use of isoxazoline derivatives as anti-bacterial agents,



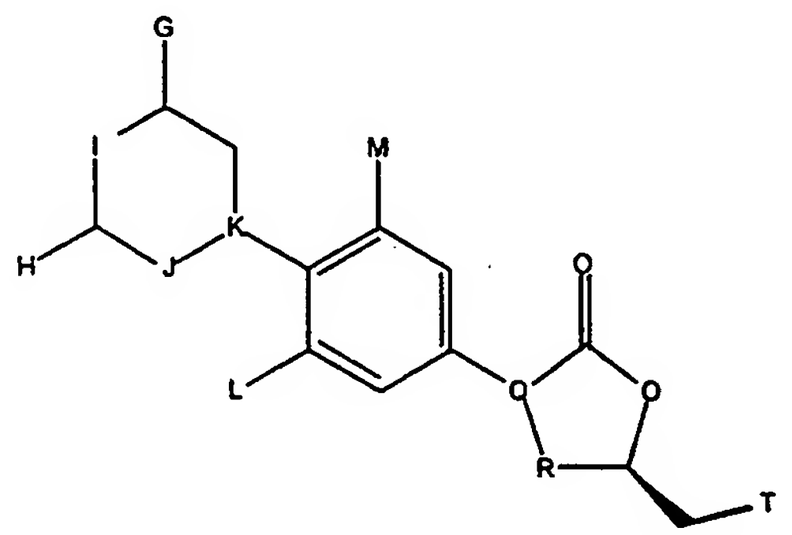
where W is a substituted aryl or heteroaryl system and V is H, or C_1-C_4 alkyl optionally substituted with F, Cl, OH, C_1-C_4 alkoxy, or acyloxy.

Oxazolidinones **II** shown below are a well known class of orally active antibacterial agents. The prior art contains numerous references to these compounds where Y and Z can include a wide variety of substituents. Specific substituted oxazolidinones are discussed in U.S. Patent Nos. 4,705,799 and 5,523,403 (substituted phenyl 2-oxazolidinones), U.S. Patent Nos. 4,948,801; 5,254,577; and 5,130,316 (arylbenzene oxazolidinyl compounds), and European Patent Applications 0,697,412; 0,694,544; 0694,543; and 0,693,491 (5 to 9-membered heteroaryl substituted oxazolidinones).



II

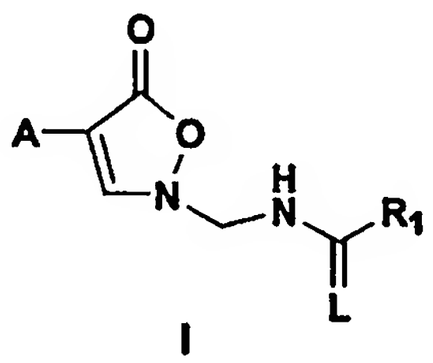
Additionally, certain compounds containing a substituted furanone ring have been reported to possess antibiotic activity. WO 97/14690 discloses



where T is hydroxy or $NHC(O)C_1$-C_4 alkyl, M and L are each independently hydrogen or fluoro, G and H are are each independently hydrogen or methyl, K-J is of the formula C=CH, CHCH2 or C(OH)CH2, I is O, SO, SO2 or a substituted nitrogen, and Q-R is CH_2-CH_2 or $CH=CH_2$. Other substituted furanones are discussed in U.S. Patent 5,708,169, WO 97/43280 and WO 97/10235.

SUMMARY OF THE INVENTION

It has now been found that certain substituted isoxazolinones are effective as antibacterial agents. Specifically, the invention covers compounds of the formula I:



I

or a pharmaceutically acceptable salt thereof wherein:

R_1 is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, or C_{1-8} acyloxy,

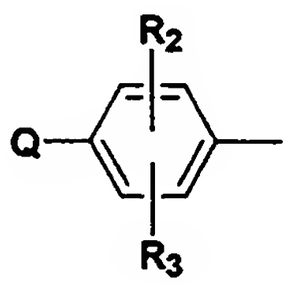
c) C_{3-6} cycloalkyl, or

d) C_{1-8} alkoxy;

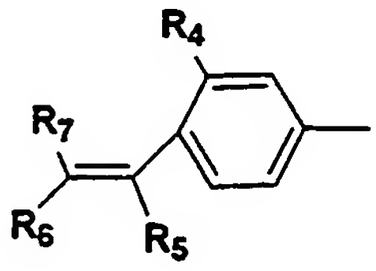
L is oxygen or sulfur;

A is

a)



b)



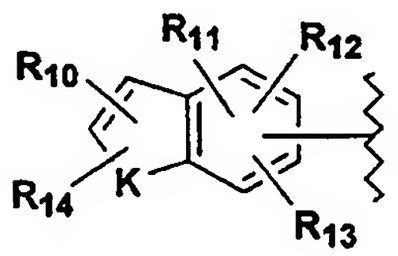
c) a 5-membered heteroaromatic moiety having one to three hetero atoms selected from the group consisting of S, N,

and O, wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom and can additionally have a fused-on benzene or naphthyl ring, and wherein the heteroaromatic moiety is optionally substituted with one to three R_8,

d) a 6-membered heteroaromatic moiety having at least one nitrogen atom, wherein the heteroaromatic moiety is bonded via a carbon atom, wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three R_9,

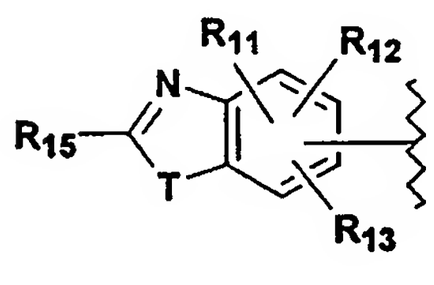
e) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_9,

f)



, or

g)



;

wherein R_2 and R_3 are each independently

a) H,

b) F,

c) Cl,

d) Br,

e) C_{1-6} alkyl,

f) NO_2,

g) I,

h) C_{1-6} alkoxy,

i) OH

j) amino,

k) cyano, or

l) R_2 and R_3 taken together are $-O(CH_2)_h-O$;

wherein R_4 is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_5 is

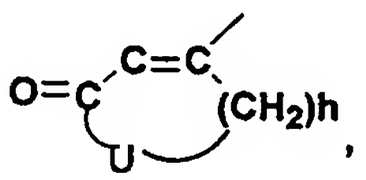
a) H,

b) CF_3,

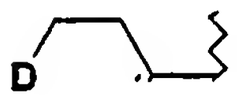
c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_5 and R_6 taken together are a 5-, 6-, or 7-membered ring of the formula,



,

f) 

— in which D is S, O or NR_{86} in which R_{86} is H or C_{1-6} alkyl, or

g) R_5 and R_6 taken together are $-(CH_2)_k-$, when R_7 is an electron-withdrawing group;

R_6 and R_7 at each occurrence are the same or different and are

a) an electron-withdrawing group,

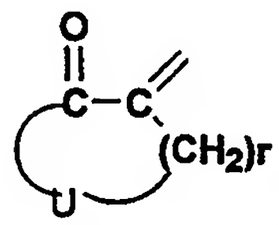
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_6 and R_7 is an electron-withdrawing group, or

f) R_6 and R_7 taken together are a 5-, 6-, or 7-membered ring of the formula,



;

U is

a) CH_2,

b) O,

c) S or,

d) NR_{16};

R_{16} is

a) H or

b) C_{1-5} alkyl;

wherein R_8 is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) $-NR_{17}R_{18}$,

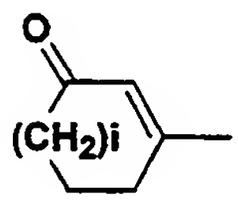
m) —C(=NOH)–R_{87} in which R_{87} is H or C_{1-6} alkyl,

n) C_{1-6} alkyl optionally substituted with OH, sulfamoyl, C_{1-5} alkoxy, C_{1-5} acyl, or –$NR_{17}R_{18}$,

o) C_{2-8} alkyl optionally substituted with one or two R_{19},

p) phenyl optionally substituted with one or two R_{19},

q) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{19}, or



;

R_{17} and R_{18} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) C_{5-6} cycloalkyl, or

d) R_{17} and R_{18} taken together with the nitrogen atom is a 5- or 6-membered saturated or unsaturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, formyl, a 5- or 6-membered heteroaromatic moiety containing 1-3 O, N or S, —C(=O)–$NR_{88}R_{89}$ in which R_{88} and R_{89} are each independently hydrogen or C_{1-6} alkyl, SO_2R_{90} in which R_{90} is H or C_{1-6} alkyl, or C_{1-3} acyl optionally substituted with 1 or more F, Cl or OH;

R_{19} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{17}R_{18}$,

m) phenyl,

n) $-C(=O)NR_{20}R_{21}$,

o) $-N\ R_{17}R_{18}$,

p) $-N(R_{20})(-SO_2R_{22})$,

q) $-SO_2-NR_{20}R_{21}$, or

r) $-S(=O)_iR_{22}$;

R_{20} and R_{21} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl, or

c) phenyl;

R_{22} is

a) C_{1-4} alkyl, or

b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_9 is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) $-NR_{23}R_{24}$,

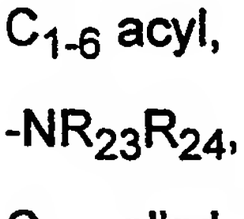
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{23}R_{24}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{25},

o) phenyl optionally substituted with one or two R_{25},

p) a 5- or 6-membered saturated or unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{25}, or

q)



,

R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{23} and R_{24} taken together with the nitrogen atom is a 5- or 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{25} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) NO_2,

h) C_{1-6} alkoxy,

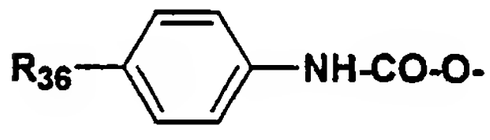
i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{32}R_{33}$, $-SR_{34}$, $-O-SO_2R_{35}$, or



,

n) $-C(=O)NR_{26}R_{27}$,

o) $-NR_{23}R_{24}$,

p) $-N(R_{26})(-SO_2R_{22})$,

q) $-SO_2-NR_{26}R_{27}$, or

r) $-S(=O)_iR_{22}$,

s) $-CH=N-R_{28}$, or

t) $-CH(OH)-SO_3R_{31}$;

R_{22} is the same as defined above;

R_{26} and R_{27} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{28} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{29}R_{30}$;

R_{29} and R_{30} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{31} is

a) H, or

b) a sodium ion;

R_{32} and R_{33} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

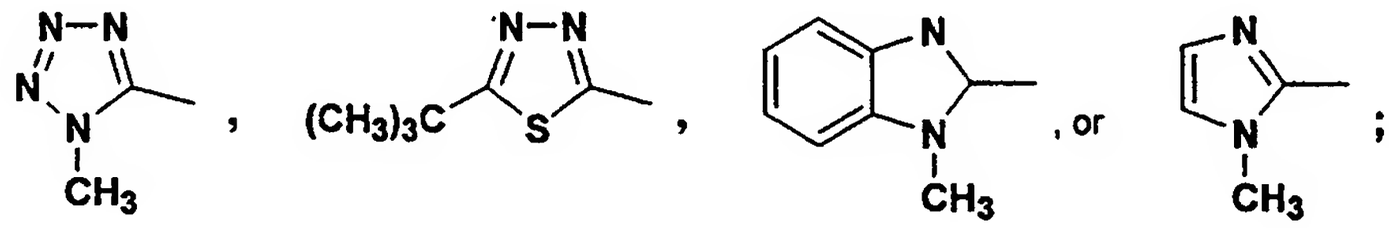
f) C_{3-6} cycloalkyl,

g) R_{32} and R_{33} taken together are a 5- or 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{37})(OR_{38})$, or

i) $-SO_2-R_{39}$;

R_{34} is



, or ;

R_{35} is C_{1-3} alkyl;

R_{36} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{37} and R_{38} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{39} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O,

b) S, or

c) NR_{40} in which R_{40} is hydrogen, formyl, C_{1-4} alkyl, C_{1-4} acyl, phenyl, C_{3-6} cycloalkyl, $-P(O)(OR_{37})(OR_{38})$ or $-SO_2-R_{39}$ in which R_{37}, R_{38} and R_{39} are as defined above;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} at each occurrence are the same or different and are

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substitutents (e) and (f) can be optionally substituted with OH, halo, C_{1-6} alkoxyl, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

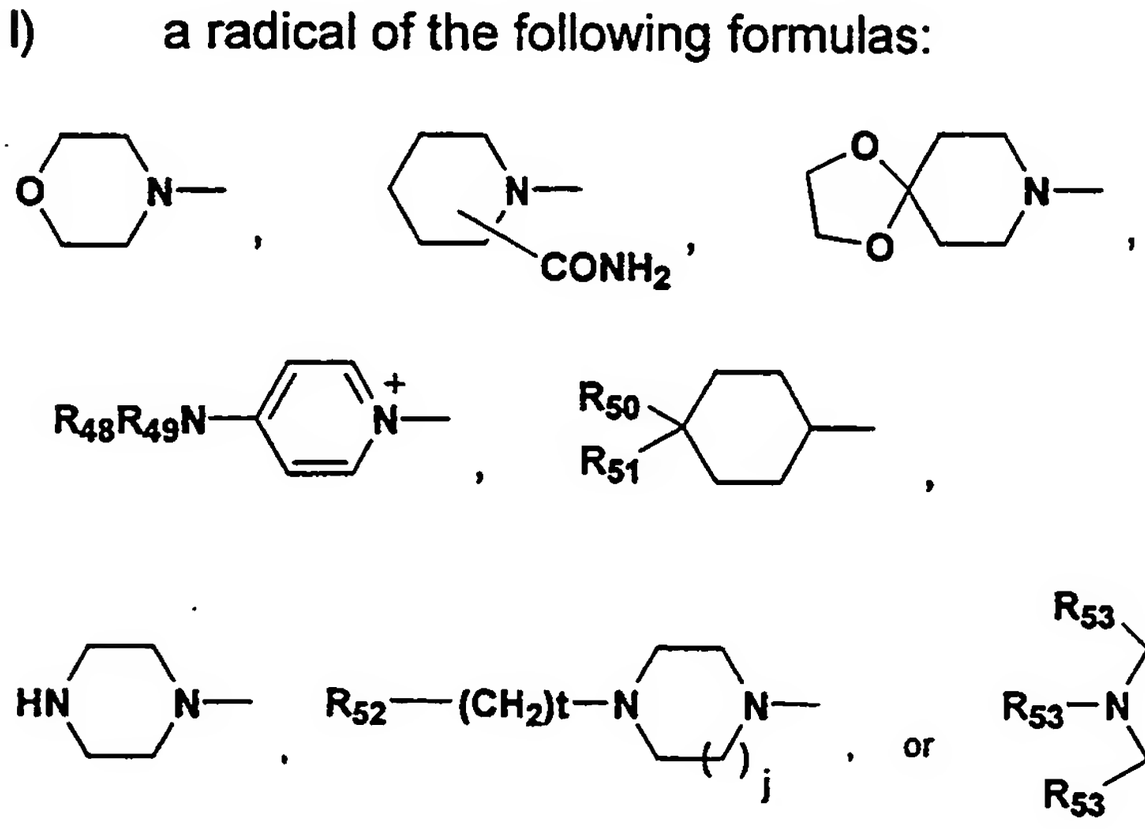
h) $-NR_{42}R_{43}$,

i) OR_{44},

j) $-S(=O)_i-R_{45}$,

k) $-SO_2-N(R_{46})(R_{47})$, or

l) a radical of the following formulas:



R_{19} is the same as defined above;

T is

a) O,

b) S, or

c) SO_2;

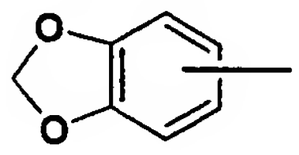
R_{42} and R_{43} at each occurrence are the same or different and are

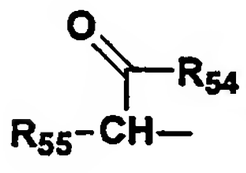
a) H,

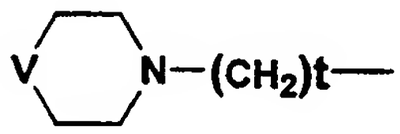
b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5- or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy,$-NR_{48}R_{49}$, or  ,

f)  , or

g)  ;

V is

a) O,

b) CH_2, or

c) NR_{56};

R_{48} and R_{49} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{54} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{57}R_{58}$;

R_{55} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{56} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{57} and R_{58} at each occurrence are the same or different and are

a) H,

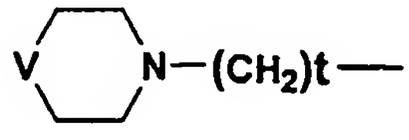
b) C_{1-5} alkyl,

c) C_{1-3} cycloalkyl, or

d) phenyl;

R_{44} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

b) 

,

c) phenyl, or

d) pyridyl;

R_{45} is

a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, or 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group of S, N, and O, wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{46} and R_{47} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{50} and R_{51} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{48}R_{49}$ in which R_{48} and R_{49} are as defined above,

d) R_{50} and R_{51} taken together are =O;

R_{52} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5- or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, wherein the substituents (a) and (b) can in turn be optionally substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

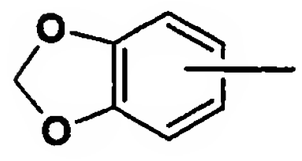
d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{48}R_{49}$ in which R_{48} and R_{49} are as defined above,

g) $-C(=O)-R_{59}$, or

h)



;

R_{53} is

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

g) $-P(O)(OR_{37})(OR_{38})$, or

h) $-SO_2R_{39}$, in which R_{37}, R_{38} and R_{39} are as defined above;

R_{59} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0, or 1;

k is 3, 4, or 5;

r is 1, 2, 3, 4, 5 or 6;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2; and

Q is

a) hydrogen,

b) halo,

c) NO_2,

d) N_3,

e) C_1-C_6 alkylthio,

f) C_1-C_6 alkyl—$\overset{O}{\overset{\|}{S}}$—,

g) C_1-C_6 alkyl—$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$—,

h) C_1-C_6 alkyl,

i) C_1-C_6 alkoxy,

j) formyl,

k) C_1-C_6 alkyl—$\overset{O}{\overset{\|}{C}}$—,

l) C_1-C_6 alkyl—O-$\overset{O}{\overset{\|}{C}}$—,

m) -sulfamoyl (H_2NSO_2-),

n) -NHOH,

o) C_1-C_6 alkyl—$\overset{O}{\overset{\|}{C}}$-O—,

p) heteroaryl —$\overset{O}{\overset{\|}{C}}$— in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

q) $C_6H_5-\overset{O}{\overset{\|}{C}}-$,

r) amino,

s) C_1-C_6 alkylamino-,

t) di (C_1-C_6 alkyl)amino-,

u) (C_1-C_6) alkyl$-\overset{O}{\overset{\|}{C}}-NR_{60}R_{61}$ in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

v) OH,

w) cyano,

x) hydroxy (C_1-C_6 alkyl),

y) C_1-C_6 alkyl$-S-\overset{O}{\overset{\|}{C}}-$,

z) $NC-(CH_2)_r-\overset{O}{\overset{\|}{C}}-$ in which r is 1-6,

aa) $C_6H_5CH_2$-$O-\overset{O}{\overset{\|}{C}}-$,

bb) C_6H_5-$O-\overset{O}{\overset{\|}{C}}-$,

cc) C_1-C_6 alkyl$-\overset{N-OR_{84}}{\overset{\|}{C}}-$ in which R_{84} is hydrogen or C_{1-6} alkyl,

dd) $R_{85}O-(CH_2)_{1-6}-\overset{O}{\overset{\|}{C}}-$ in which R_{85} is hydrogen, C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy or C_{1-8} acyloxy, C_{3-6} cycloalkyl or C_{1-8} alkoxy;

ee) $H-\overset{N-OR_{84}}{\overset{\|}{C}}-$ in which R_{84} is hydrogen or C_{1-6} alkyl,

ff) a substituted or unsubstituted C_6-C_{10} aryl moiety,

gg) a substituted or unsubstituted monocyclic or bicyclic, saturated or unsaturated, heterocyclic moiety having 1-3

atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent,

hh) a monocyclic or bicyclic substituted or unsubstituted heteroaromatic moiety having 1-3 hetero atoms selected from O, N or S, said ring being bonded via a ring carbon or nitrogen to the phenyl substituent and wherein the heteroaromatic moiety can additionally have a fused-on benzene or naphthalene ring;

the substituents for such p, q, ff, gg and hh moieties being selected from 1 or 2 of the following:

1) halo,

2) C_{1-6} alkyl,

3) NO_2,

4) N_3,

5) C_1-C_6 alkyl $-\overset{O}{\overset{\|}{S}}-$,

6) C_1-C_6 alkyl $-\overset{O}{\overset{\|}{S}}(=O)-$,

7) formyl,

8) C_1-C_6 alkyl $-\overset{O}{\overset{\|}{C}}-$,

9) C_1-C_6 alkyl $-O-\overset{O}{\overset{\|}{C}}-$,

10) heteroaryl $-\overset{O}{\overset{\|}{C}}-$ in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

11) $C_6H_5-\overset{O}{\overset{\|}{C}}-$,

12) -(C_1-C_6) alkyl $-\overset{O}{\overset{\|}{C}}-NR_{60}R_{61}$ in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

13) OH,

14) hydroxy (C_1-C_6 alkyl),

15) C_1-C_6 alkyl—S-C(=O)—,

16) NC-$(CH_2)_r$—O-C(=O)— in which r is 1-6,

17) $C_6H_5CH_2$—O-C(=O)—,

18) -CH_2-R_{80} in which R_{80} is

a) -OR_{32} in which R_{32} is as defined above,

b) -SR_{32} in which R_{32} is as defined above,

c) -$NR_{32}R_{33}$ in which R_{32} and R_{33} are as defined above, or

d) 5- or 6-membered heteroaromatic containing 1-4 O, S or N atoms,

19) C_1-C_6 alkyl—C(=N-OR_{84})— in which R_{84} is as defined above,

20) cyano,

21) carboxyl,

22) CF_3,

23) C_1-C_6 alkyl—C(=O)-O—,

24) C_6H_5-O-C(=O)— in which the phenyl moiety may be optionally substituted by halo or (C_1-C_6)alkyl,

25) $NR_{60}R_{61}$—C(=O)— in which R_{60} and R_{61} are as defined above,

26) R_{91}-NH-C(=O)— or R_{91}-C(=O)-NH— in which R_{91} is a 5- or 6-membered aromatic heterocyclic group having 1-3 O, N or S,

27) $C_6H_5(CH_2)_{1-6}-O-\overset{O}{\overset{\|}{C}}-$,

28) $R_{85}O-(CH_2)_{1-6}-O-\overset{O}{\overset{\|}{C}}-$ in which R_{85} is as defined above,

29) $SiR_{99}R_{100}R_{101}-O-CH_2-\overset{O}{\overset{\|}{C}}-$ in which R_{99}, R_{100} and R_{101} are each independently C_{1-6} alkyl; or

Q and either R_1 and R_2 taken together form $-O-CH_2-O$.

The compounds of this invention are novel and represent a new class of antibacterial agents. They are distinct from both the previously reported oxazolidinone and isoxazoline antibiotics since they incorporate the isoxazolinone ring system. They differ from the prior art isoxazolinone herbicides since the ring nitrogen must be substituted with an amide moiety as defined above.

The compounds of formula I are antibacterial agents useful in the treatment of infections in humans and other animals caused by a variety of bacteria, particularly methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium.

Also included in the invention are processes for preparing the compounds of formula I and pharmaceutical compositions containing said compounds in combination with pharmaceutically acceptable carriers or diluents.

DEFINITIONS

The term "pharmaceutically acceptable salt" as used herein is intended to include the non-toxic acid addition salts with inorganic or organic acids, e.g. salts with acids such as hydrochloric, phosphoric, sulfuric, maleic, acetic, citric, succinic, benzoic, fumaric, mandelic, p-toluene-sulfonic, methanesulfonic, ascorbic, lactic, gluconic, trifluoroacetic, hydroiodic, hydrobromic, and the like. These salts may be in hydrated form.

The terms "halo" or "halogen" includes chloro, bromo, fluoro and iodo, and is preferably chloro or fluoro.

The aliphatic "alkyl" groups as used herein means straight or branched chains having the specified number of carbon atoms, e.g. in the case of C_1-C_6 alkyl, the alkyl group may have from 1 to 6 carbon atoms.

Similarly, terms such as "C_2-C_8 alkenyl" refer to at least one double bond alkenyl group having the specified number of carbon atoms, "C_2-C_8 alkenyl" refers to at least one triple bond alkynyl group having the specified number of carbons, etc.

The term "acyloxy" unless otherwise defined refers to a group of the type $CH_3\overset{O}{\overset{\|}{C}}-O-$ where the alkyl group can have the specified number of carbon atoms, e.g. C_1-C_6 alkoxy would have 1-6 carbons. Where not specified the carbon length is from 1-6 carbons.

Unless otherwise indicated the term "aryl" refers to aromatic carbocyclic rings, i.e. phenyl and naphthyl.

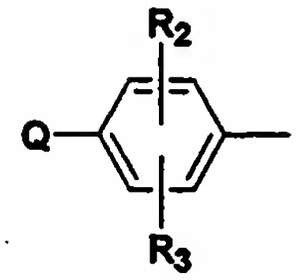
"Heteroaromatic" as used herein refers to an aromatic heterocyclic moiety having one or more atoms selected from O, N, S, e.g. pyridine, thiophene, furan, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyn, 3-quinolyn, 1-isoquinolyl, 3-isoquinolyl, 2-imadazolyl, 4-imadazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5- thiazolyl, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-thiazol-3-yl, 1,2,4-thiazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl.

A saturated or unsaturated heterocyclic group can have 1-3 atoms selected from O, N and S, e.g. dioxolane, imidazolidine, dithiolane, oxathiolane, oxazolidine, piperidinyl, piperazinyl, morpholino or thiomorpholino, or the corresponding unsaturated heterocyclic groups.

Where possible nitrogen and/or sulfur atoms in such heterocyclic moieties may be oxidized and such oxidized compounds are intened to be encompassed within the formula I compounds.

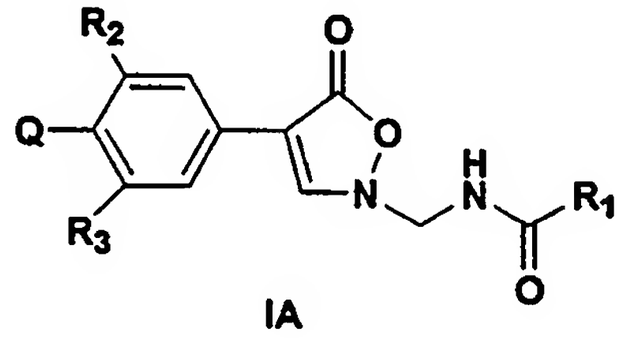
DETAILED DESCRIPTION

Preferred embodiments of the present invention are the compounds of formula I wherein A is



in which Q_1, R_2, and R_3 are as defined above.

A still more preferred embodiment of the present invention comprises a compound of the formula



IA

or a pharmaceutically acceptable salt thereof, in which

R_1 is H, C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, or C_{1-8} acyloxy, C_{3-6} cycloalkyl or C_{1-8} alkoxy;

R_2 and R_3 are each independently

a) H,

b) F,

c) Cl,

d) Br,

e) C_{1-6} alkyl,

f) NO_2,

g) I,

h) C_{1-6} alkoxy,

i) OH

j) amino, or

k) cyano; and

Q is

a) hydrogen,

b) halo,

c) NO_2,

d) N_3,

e) C_1-C_6 alkylthio,

f) C_1-C_6 alkyl $-\overset{\overset{O}{\|}}{S}-$,

g) C_1-C_6 alkyl$-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$,

h) C_1-C_6 alkyl,

i) C_1-C_6 alkoxy,

j) formyl,

k) C_1-C_6 alkyl$-\overset{\overset{O}{\|}}{C}-$,

l) C_1-C_6 alkyl$-O-\overset{\overset{O}{\|}}{C}-$,

m) C_1-C_6 alkyl$-\overset{\overset{O}{\|}}{C}-O-$,

n) heteroaryl$-\overset{\overset{O}{\|}}{C}-$ in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

o) $C_6H_5-\overset{\overset{O}{\|}}{C}-$,

p) amino,

q) C_1-C_6 alkylamino-,

r) di(C_1-C_6 alkyl)amino-,

s) (C_1-C_6) alkyl$-\overset{\overset{O}{\|}}{C}-NR_{60}R_{61}$,in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

t) OH,

u) cyano,

v) hydroxy (C_1-C_6 alkyl),

w) C_1-C_6 alkyl—S-C(=O)—,

x) NC—$(CH_2)_r$—O-C(=O)— in which r is 1-6,

y) $C_6H_5CH_2$—O-C(=O)—,

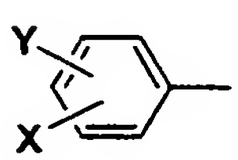
z) C_6H_5—O-C(=O)—,

aa) C_1-C_6 alkyl—C(=N-OR_{84})— wherein R_{84} is hydrogen or C_{1-6} alkyl,

bb) $R_{85}O$-$(CH_2)_{1-6}$—C(=O)— in which R_{85} is hydrogen, C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy or C_{1-8} acyloxy, C_{3-6} cycloalkyl or C_{1-8} alkoxy,

cc) H-C(=N-OR_{84})— in which R_{84} is as defined above,

dd)



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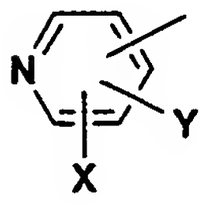

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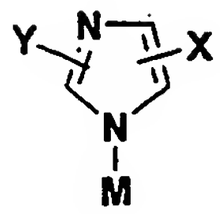

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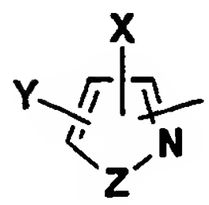

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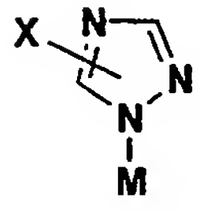

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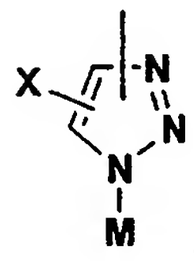

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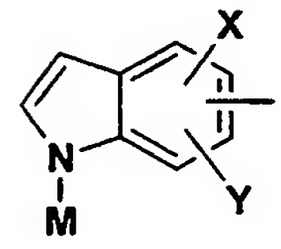

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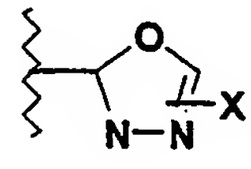

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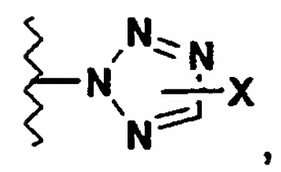

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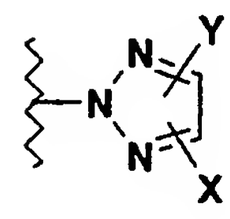

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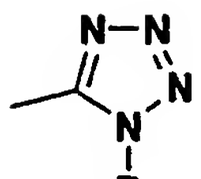

in which R_{92} is H or C_{1-6} alkyl,

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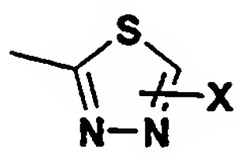

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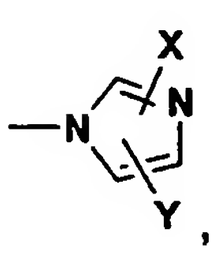

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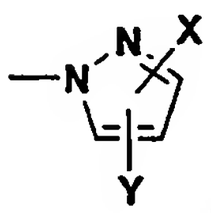

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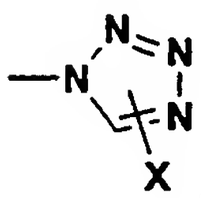

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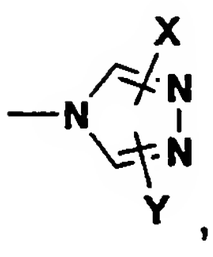

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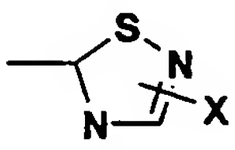

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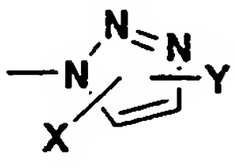

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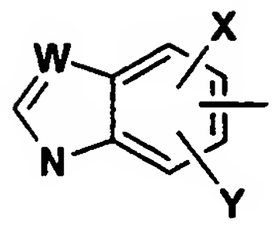

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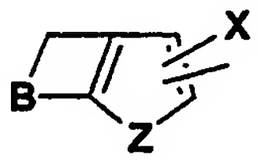

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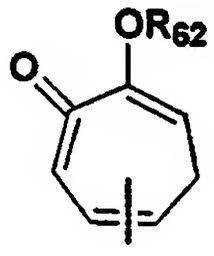

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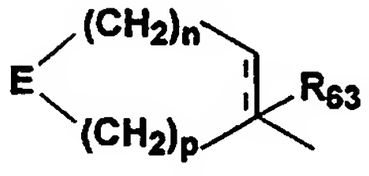


,

aaa) a diazinyl group optionally substituted with X and Y,

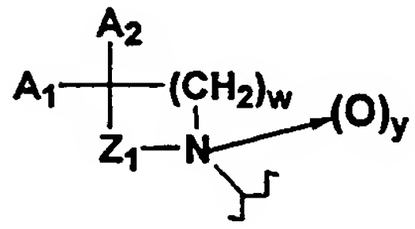
bbb) a triazinyl group optionally substituted with X and Y,

ccc) a quinolinyl group optionally substituted with X and Y,

ddd) a quinoxalinyl group optionally substituted with X and Y,

eee) a naphthyridinyl group optionally substituted with X and Y,

fff)



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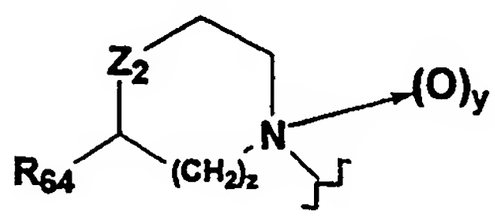

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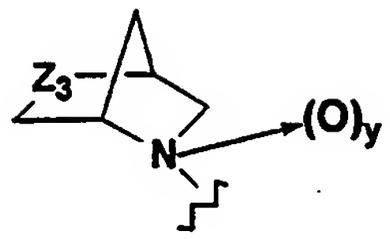
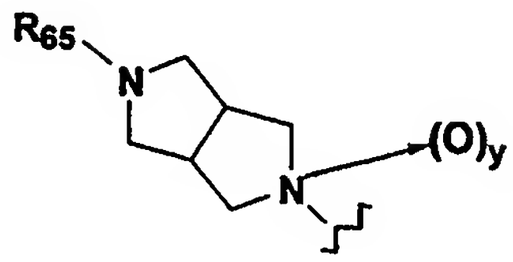


, or

iii)



;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{66}$, or

e) $-(CH_2)_nNR_{67}R_{68}$;

Z is

a) O,

b) S or

c) NM;

W is

a) CH,

b) N or

c) S or O when Z is NM;

X and Y are each independently

a) hydrogen,

b) halo,

c) NO_2,

d) N_3,

e) C_{1-6} alkythio,

f) C_1-C_6 alkyl—S(=O)—,

g) C_1-C_6 alkyl—S(=O)(=O)—,

h) C_1-C_6 alkyl,

i) C_1-C_6 alkoxy,

j) formyl,

k) C_1-C_6 alkyl—C(=O)—,

l) C_1-C_6 alkyl—O-C(=O)—,

m) heteroaryl—C(=O)— in which heteroaryl is a 5- or 6-membered aromatic heterocyclic group having 1-3 hetero atoms selected from O, N or S,

n) C_6H_5–C(=O)—,

o) amino,

p) C_1-C_6 alkylamino-,

q) di(C_1-C_6 alkyl)amino-,

r) -(C_1-C_6) alkyl—C(=O)–$NR_{60}R_{61}$ in which R_{60} and R_{61} are each independently hydrogen or C_1-C_6 alkyl,

s) OH,

t) hydroxy (C_1-C_6 alkyl),

u) C_1-C_6 alkyl—S–C(=O)—,

v) NC–$(CH_2)_r$—O-C(=O)— in which r is 1-6,

w) $C_6H_5CH_2$—O-C(=O)—,

x) $C_6H_5-O-\overset{O}{\overset{\|}{C}}-$,

y) C_1-C_6 alkyl$-\overset{N-OR_{84}}{\overset{\|}{C}}-$ in which R_{84} is as defined above,

z) cyano,

aa) carboxyl,

bb) CF_3,

cc) mercapto,

dd) C_1-C_6 alkyl$-\overset{O}{\overset{\|}{C}}-O-$,

ee) $C_6H_5-O-\overset{O}{\overset{\|}{C}}-$ in which the phenyl moiety may be optionally substituted by halo or C_1-C_6 alkyl,

ff) $C_6H_5(CH_2)_{1-6}-O-\overset{O}{\overset{\|}{C}}-$,

gg) $R_{85}O-(CH_2)_{1-6}-\overset{O}{\overset{\|}{C}}-$ in which R_{85} is as defined above, or

hh) $SiR_{99}R_{100}R_{101}-O-CH_2-\overset{O}{\overset{\|}{C}}-$ in which R_{99}, R_{100} and R_{101} are each independently C_{1-6} alkyl; or

Q and either R_1 and R_3 taken together form $-O-CH_2-O$;

R_{62} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-8} alkoxy;

E is

a) NR_{69},

b) $-S(=O)_i$ in which i is 0, 1 or 2, or

c) O;

R_{63} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) halo;

R_{66} is H or C_{1-4} alkyl;

R_{67} and R_{68} are each independently H or C_{1-4} alkyl, or $NR_{67}R_{68}$ taken together are $-(CH_2)_m-$;

R_{69} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{81}$,

e) COR_{82},

f) $-C(=O)-(CH_2)_q-C(=O)R_{81}$,

g) $-S(=O)_z-C_{1-6}$ alkyl,

h) $-S(=O)_z-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het in which j is 0 or 1;

Z_1 is

a) $-CH_2-$, or

b) $-CH(R_{70})-CH_2-$;

Z_2 is

a) $-O_2S-$,

b) -O-,

c) -S-,

d) -SO-, or

e) $-N(R_{71})-$;

Z_3 is

a) S,

b) SO,

c) SO_2, or

d) O;

A_1 is H or CH_3;

A_2 is

a) H,

b) OH-,

c) CH_3CO_2-,

d) CH_3-,

e) CH_3O-,

f) $R_{72}O$-CH_2-C(O)-NH-,

g) $R_{73}O$-C(O)-NH-,

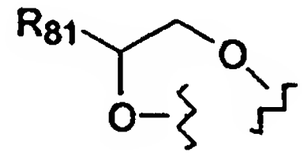
h) R_{73}-C(O)-NH-,

i) (C_1-C_2)alkyl-O-C(O)-, or

j) HO-CH_2; or

A_1 and A_2 taken together are

a)



or

b) O = ;

R_{64} is H or CH_3-;

m is 4 or 5;

n is 0, 1, 2, 3, 4 or 5;

y is 0 or 1;

p is 0, 1, 2, 3, 4 or 5;

w is 1, 2 or 3;

q is 1, 2, 3 or 4;

z is 0 or 1;

R_{65} is

a) $R_{74}OC(R_{75})(R_{76})$-C(O)-,

b) $R_{77}OC(O)$-,

c) $R_{78}(O)$-,

d) R_{79}-SO_2-, or

e) R_{80}-NH-C(O)-;

R_{70} is H or (C_1-C_3)alkyl;

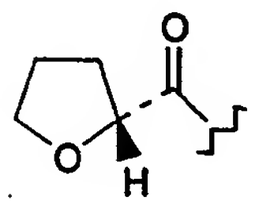
R_{71} is

a) $R_{74}OC(R_{75})(R_{76})$-C(O)-,

b) R_{77}O-C(O)-,

c) R_{78}-C(O)-,

d)



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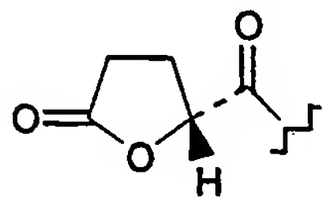
e)



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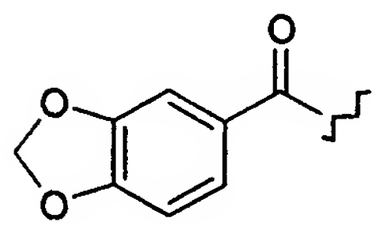
f) H_3C-C(O)-$(CH_2)_2$-C(O)-,

g) R_{79}-SO_2-,

h)



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i) R_{80}-NH-C(O)-,

R_{72} is

a) H,

b) CH_3,

c) phenyl -CH_2-, or

d) $CH_3C(O)$-;

R_{73} is (C_1-C_3)alkyl or phenyl;

R_{74} is H, CH_3, phenyl-CH_2- or CH_3-C(O)-;

R_{75} and R_{76} are each independently H or CH_3, or R_{75} and R_{76} taken together are –CH_2CH_2-;

R_{77} is (C_1-C_3)alkyl or phenyl;

R_{78} is H, (C_1-C_4)alkyl, aryl-$(CH_2)_n1$, ClH_2C, Cl_2HC, FH_2C-, F_2HC- or (C_3-C_6)cycloalkyl;

R_{79} is CH_3; -CH_2Cl, -$CH_2CH{=}CH_2$, aryl or -CH_2CN;

R_{80} is –$(CH_2)_n1$-aryl where n^1 is 0 or 1;

R_{81} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo or CN,

c) -$(CH_2)_q$–aryl in which q is as defined above, or

d) -$(CH_2)_q$–OR_{83} in which q is as defined above;

R_{82} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo or CN,

b) -$(CH_2)_q$-aryl in which q is as defined above, or

c) -$(CH_2)_q$-OR_{83} in which q is as defined above;

R_{83} is

a) H,

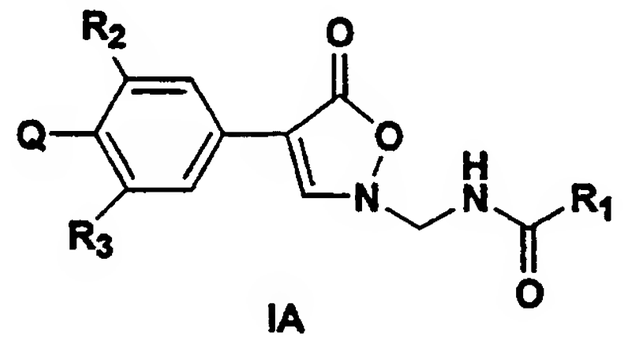
b) C_{1-6} alkyl,

c) -$(CH_2)_q$-aryl in which q is as defined above; or

d) -C(=O) C_{1-6} alkyl; and

aryl is phenyl, pyridyl or naphthyl, said phenyl, pyridyl or naphthyl moieties being optionally substituted by one or more halo, -CN, OH, SH, C_{1-6} alkoxy or C_{1-6} alkylthio.

Another preferred embodiment of the present invention comprises a compound of the formula



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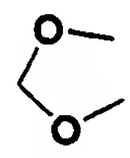
or a pharmaceutically acceptable salt thereof, in which

R_1 is H, C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy or C_{1-8} acyloxy, C_{3-6} cycloalkyl or C_{1-8} alkoxy;

R_2 and R_3 are each independently H or F; or R_2 and R_3 taken together represent



;

Q is

a) hydrogen,

b) halo,

c) N_3,

d) NO_2,

e) C_1-C_6 alkylthio,

f) C_1-C_6 alkyl—S(=O)—,

g) C_1-C_6 alkyl—S(=O)(=O)—,

h) C_1-C_6 alkyl,

i) C_1-C_6 alkoxy,

j) formyl,

k) C_1-C_6 alkyl—C(=O)—,

l) C_1-C_6 alkyl—O-C(=O)—,

m) C_1-C_6 alkyl—C(=O)-O—,

n) $(C_1$-C_6 alkoxy$)_2$N-,

o) 5- or 6-membered heterocyclic containing 1-3 O, N or S and linked to the phenyl substituent via a carbon or nitrogen, said heterocycle moiety being optionally substituted by R_{96},

p) C_1-C_6 alkyl—C(=N-OH),

q) phenyl optionally substituted by R_{96}, or

r) 5- or 6-membered saturated or unsaturated heterocyclic containing 1-3 O, N or S and linked to the phenyl substituent via a carbon or nitrogen, said heterocycle moiety being optionally substituted by R_{96}, and

R_{96} is

a) C_1-C_6 alkyl-OH,

b) C_1-C_6 alkyl—O-C(=O)—,

c) CH_3—C(=O)— C_1-C_6 alkyl—C(=O)—,

d) cyano,

e) formyl,

f) H-C(=N-OH)—,

g) C_1-C_6 alkyl—O-C(=O)—,

h) $SiR_{99}R_{100}R_{101}-O-CH_2-\overset{O}{\overset{\|}{C}}-$ in which R_{99}, R_{100} and R_{101} are each independently C_{1-6} alkyl,

i) $CH_3-\overset{O}{\overset{\|}{S}}(=O)-$ C_1-C_6 alkyl$-\overset{O}{\overset{\|}{S}}(=O)-$,

j) $HC\equiv CCH_2O\overset{O}{\overset{\|}{C}}-$,

k) $C_6H_5-O-\overset{O}{\overset{\|}{C}}-$ where the phenyl may be optionally substituted by halo,

l) $HO-CH_2-\overset{O}{\overset{\|}{C}}-$,

m) $(C_1$-C_6 alkyl$)_2N$-,

n) C_1-C_6 alkyl-NH-,

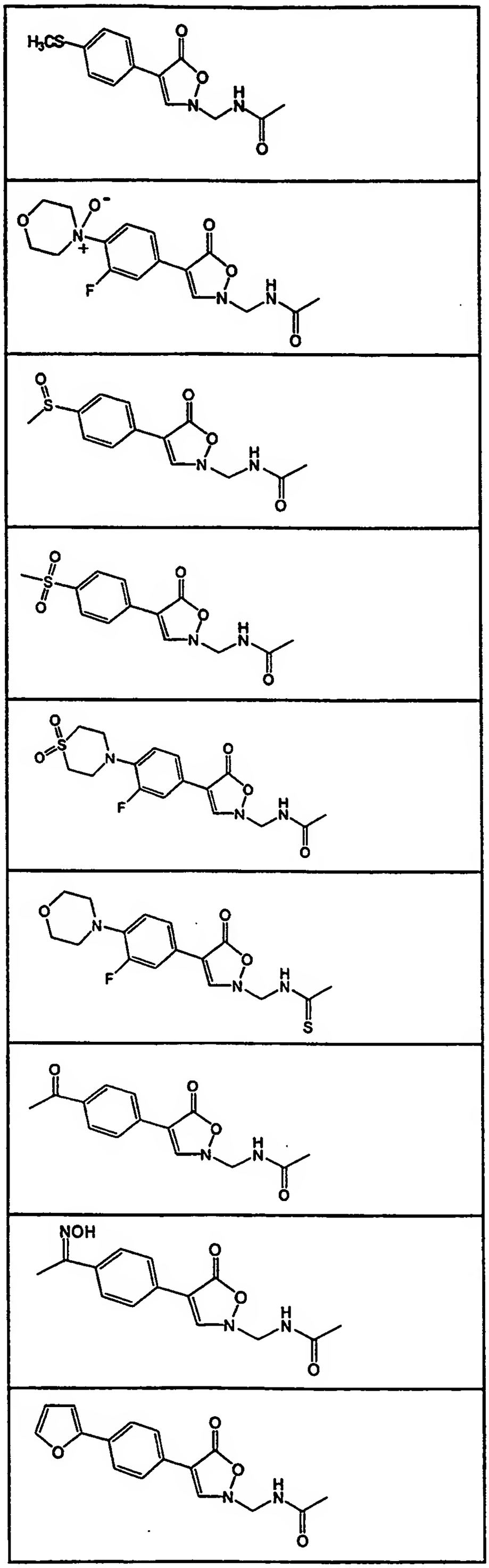
o) amino,

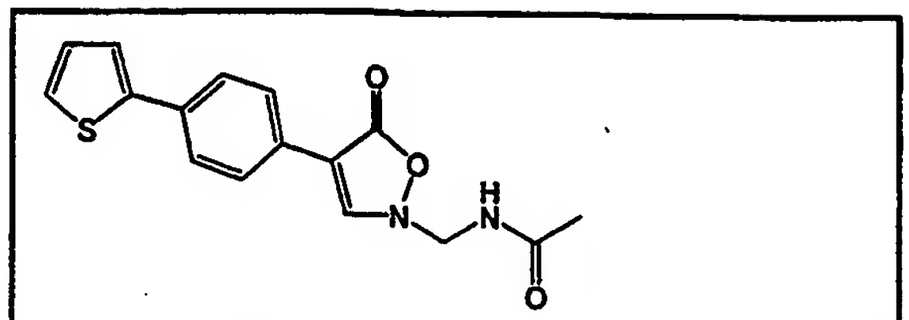
p) C_1-C_6 alkyl$-\overset{O}{\overset{\|}{S}}-$,

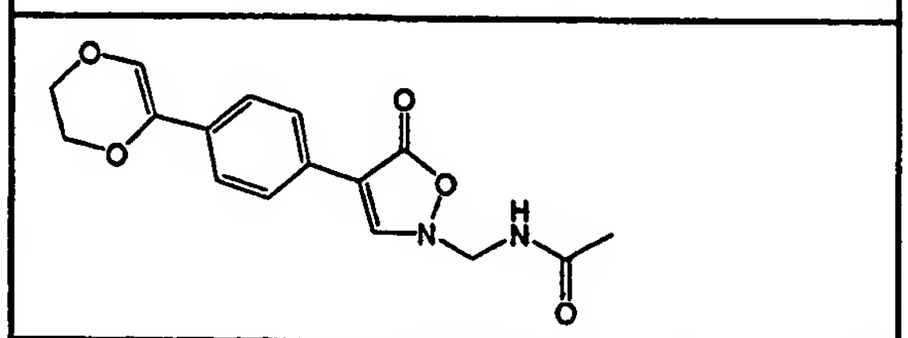
q) $C_6H_5CH_2O\overset{O}{\overset{\|}{C}}-$, or

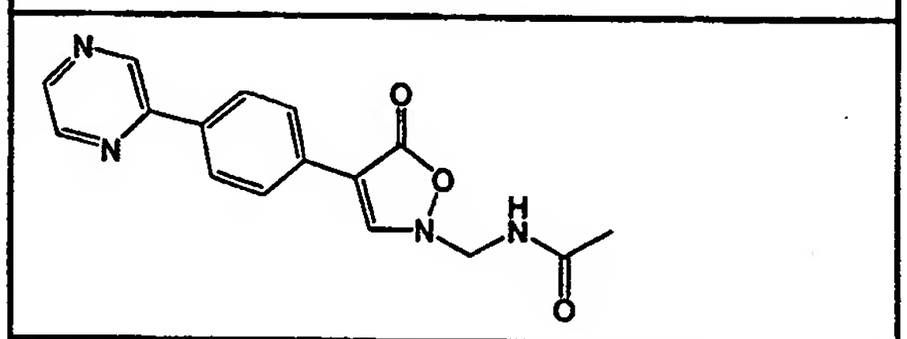
r) $R_{98}-\overset{O}{\overset{\|}{C}}-$ in which R_{98} is phenyl, 5- or 6-membered heteroaryl containing 1-3 O, N or S and linked to the phenyl substituent via a ring carbon atom or 5- or 6-membered saturated or unsaturated heterocyclic containing 1-4 O, N or S and linked to the phenyl substituent via a ring carbon atom.

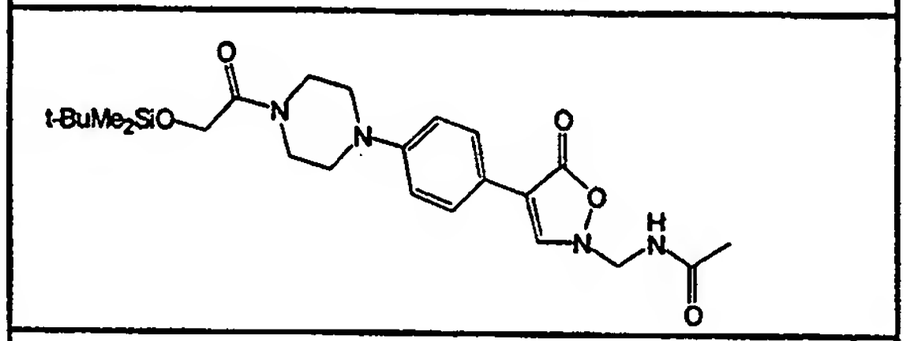
Some specific preferred embodiments of the present invention are listed in the table below.

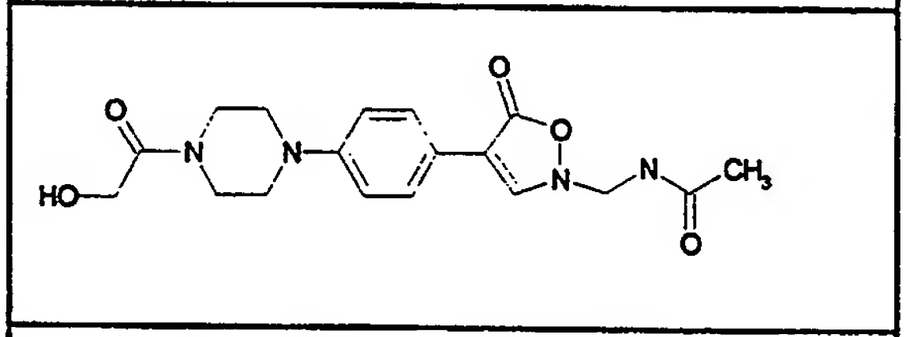


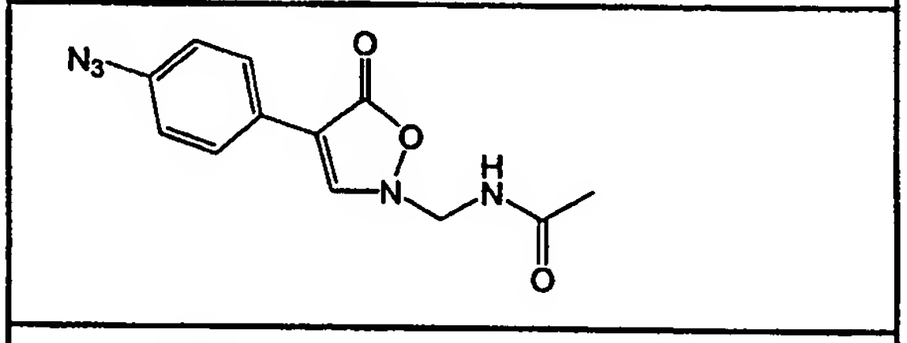


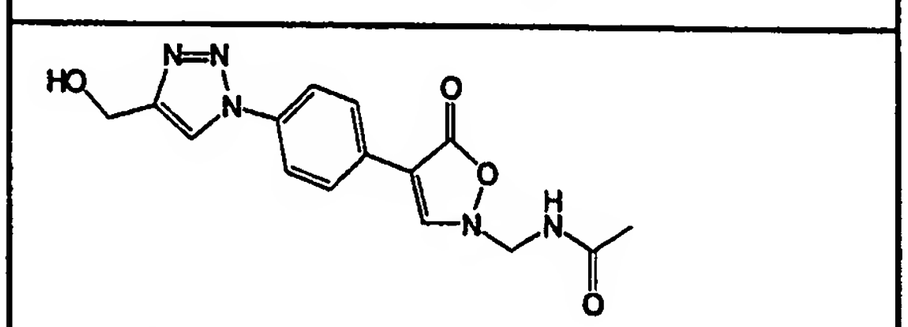


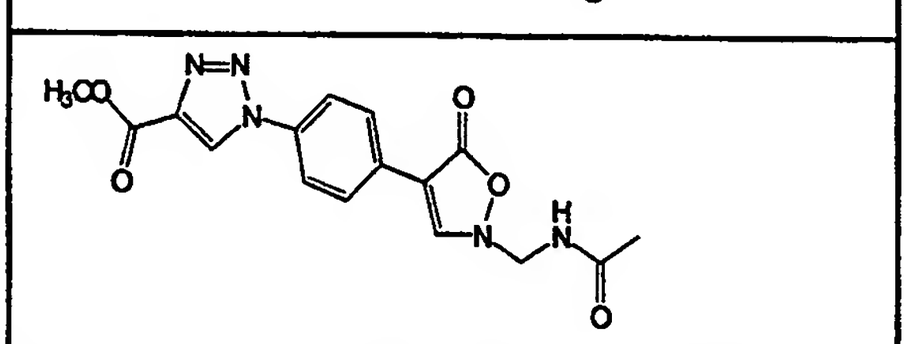


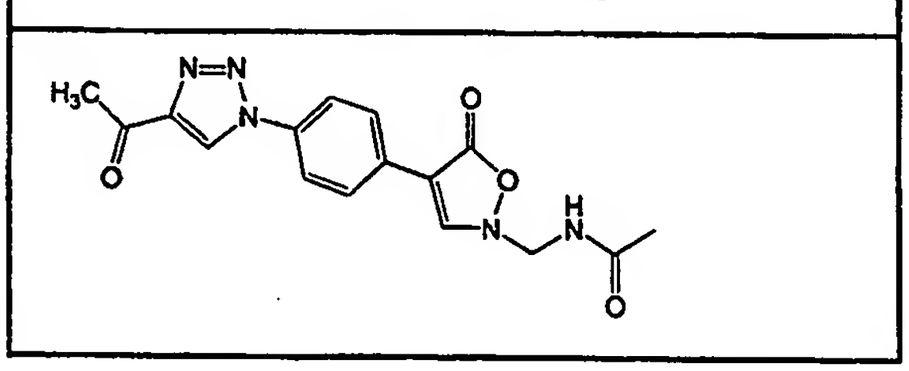


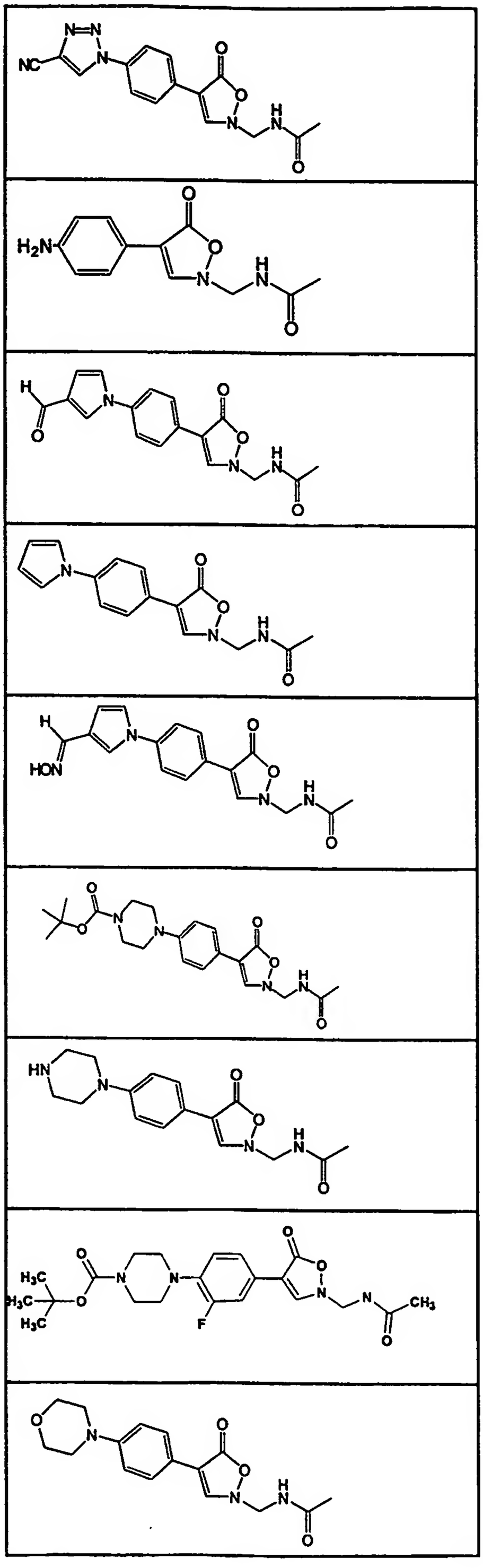


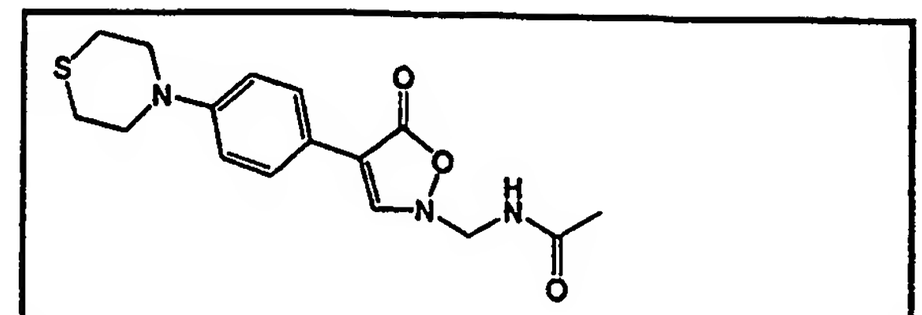


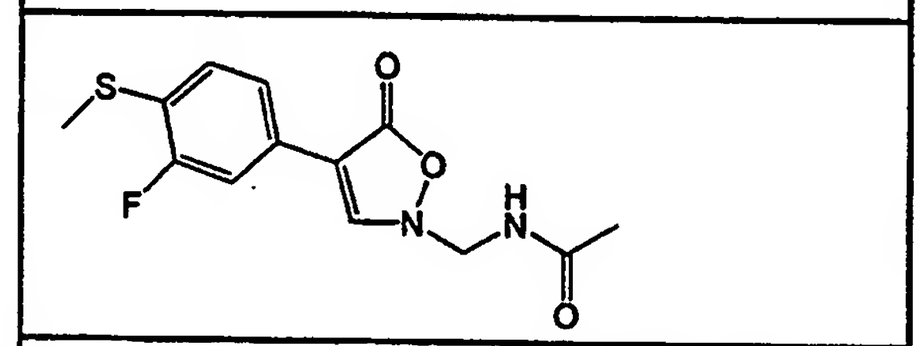


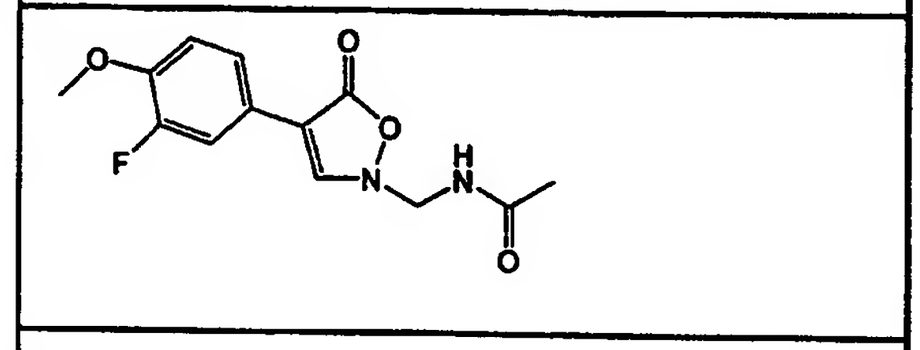


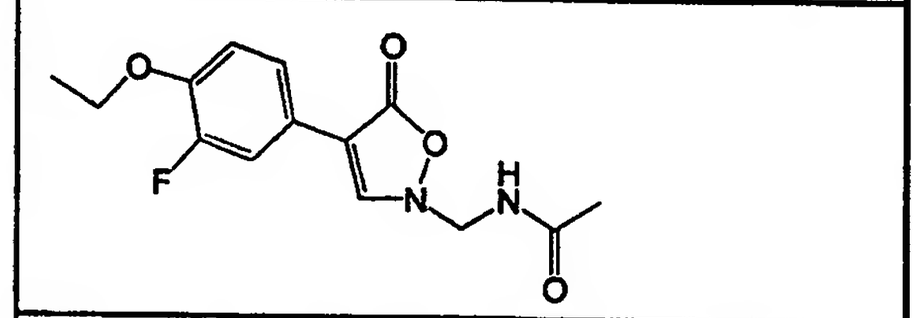


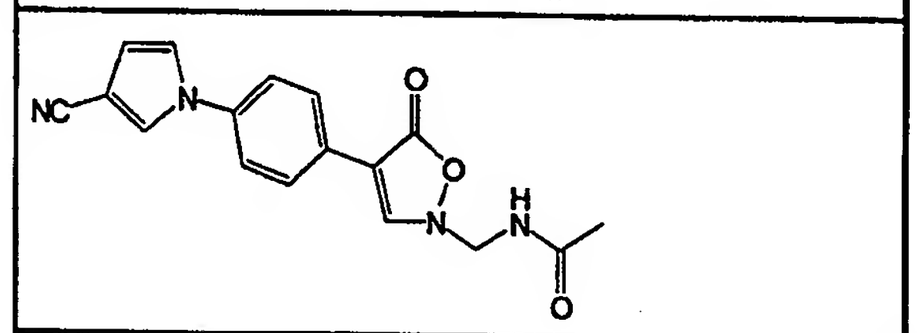


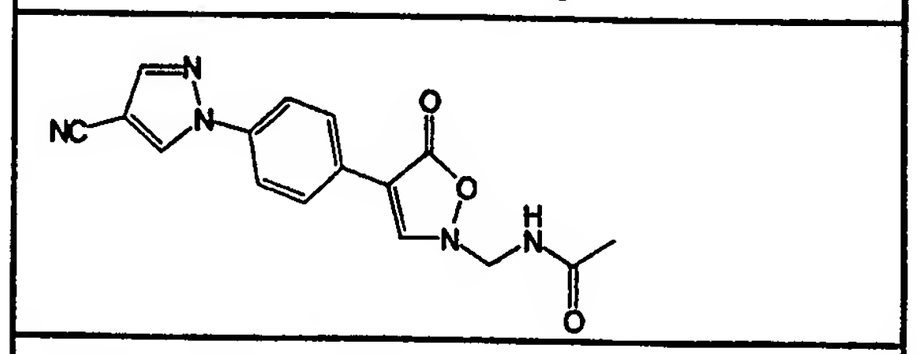


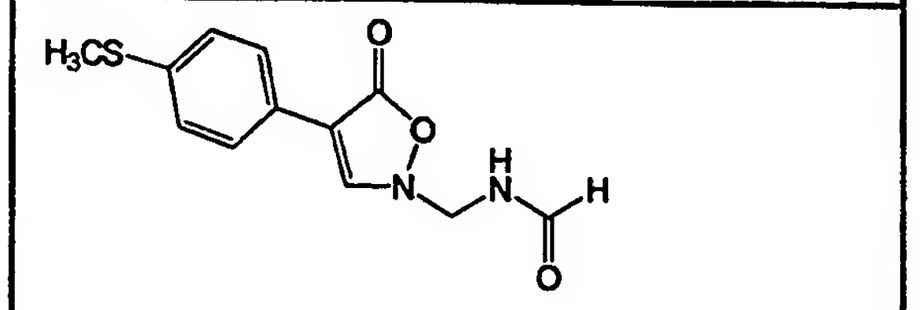


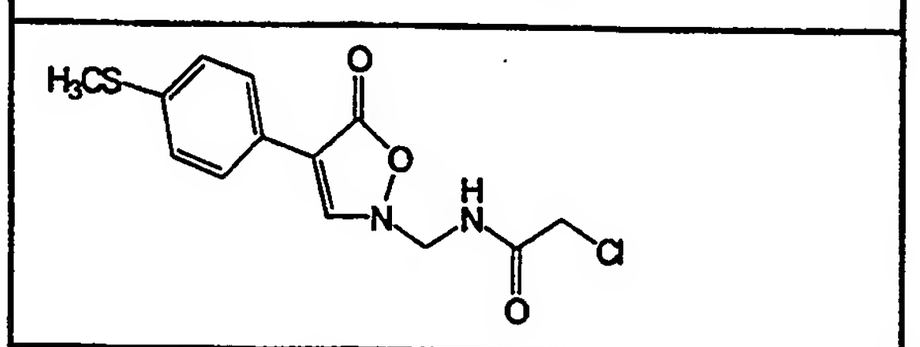


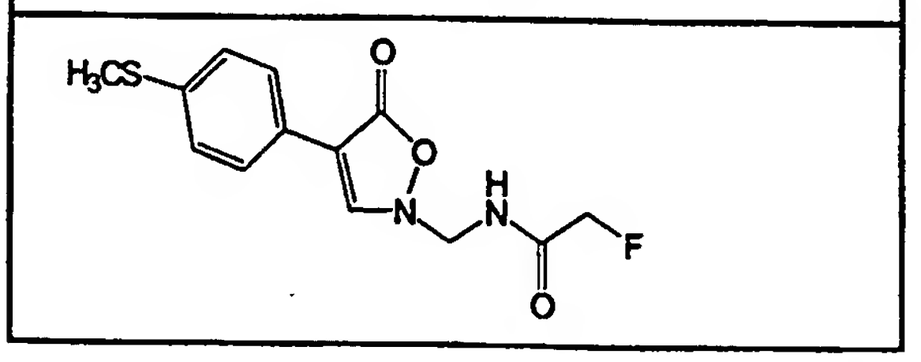


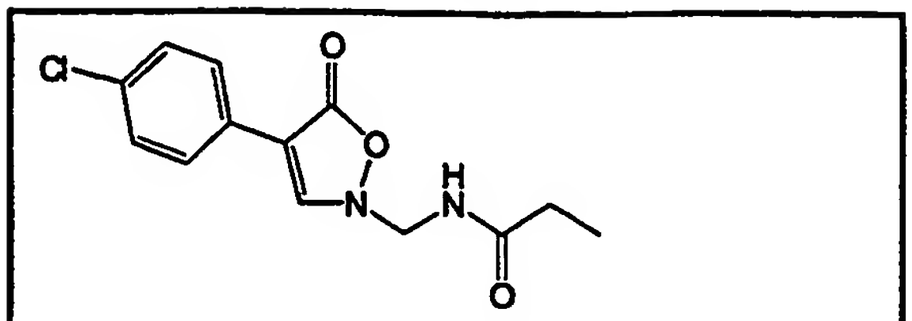


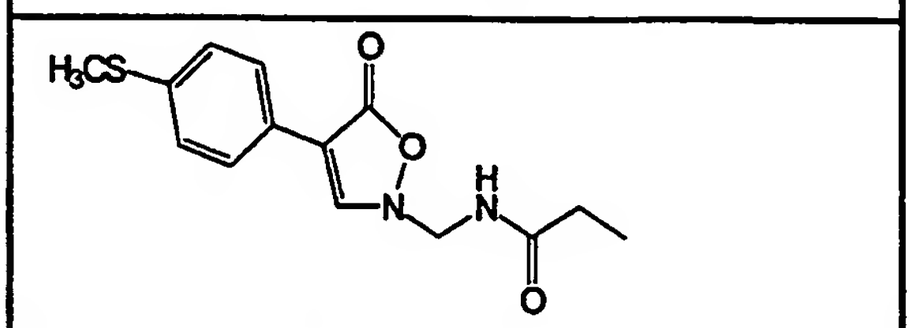


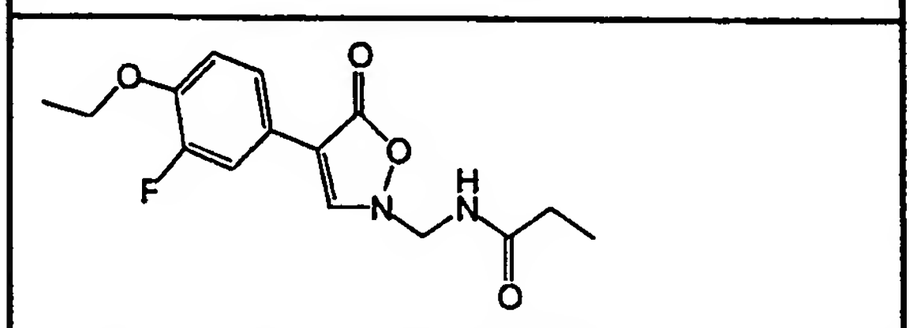


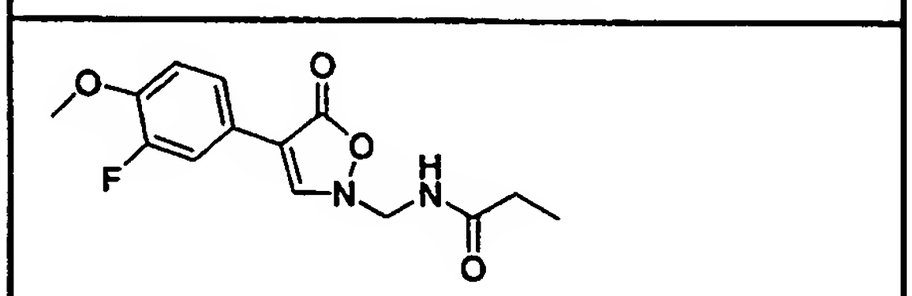


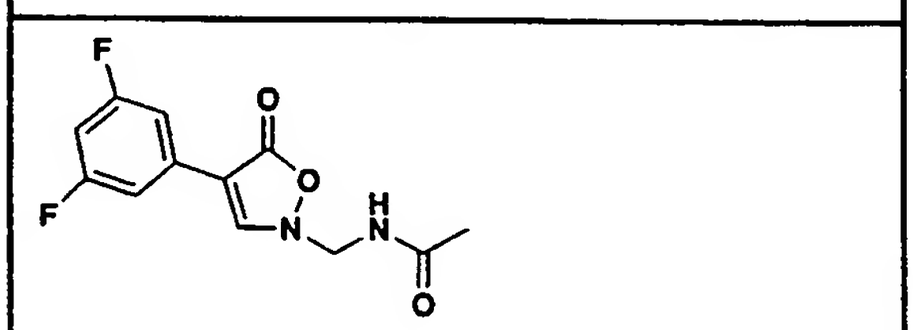


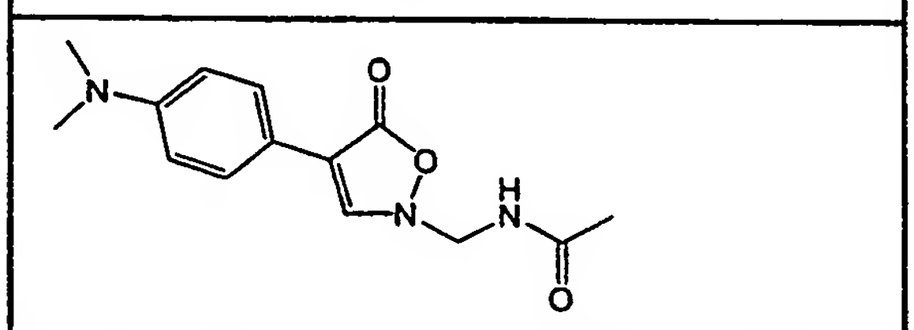


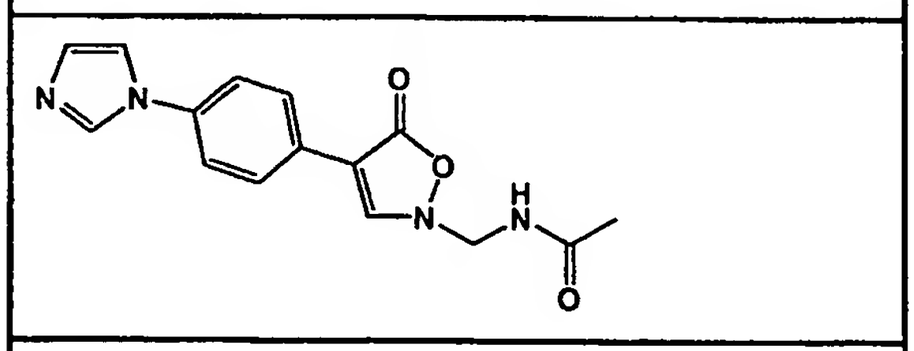


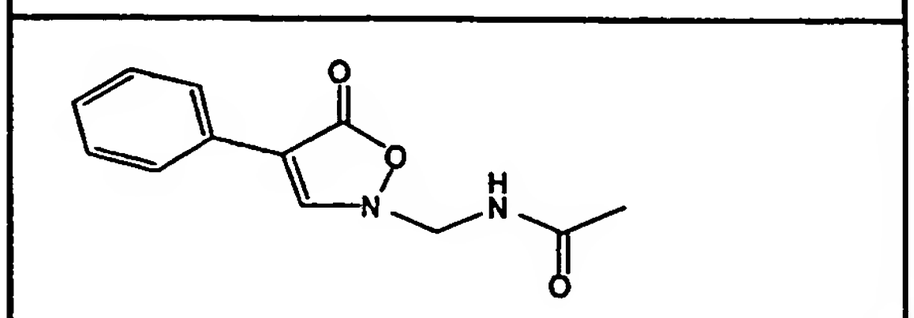


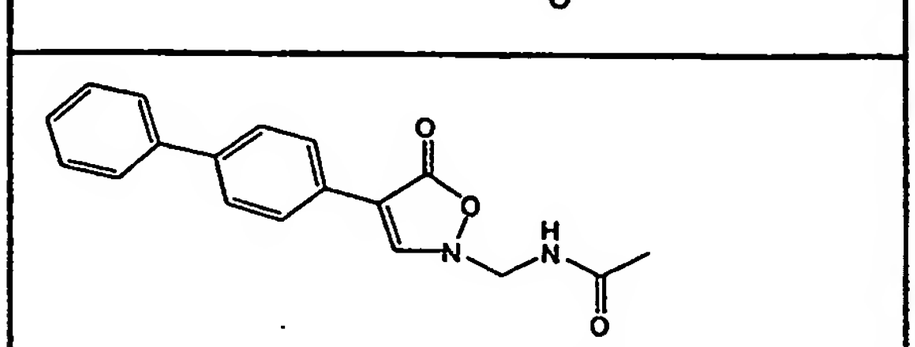


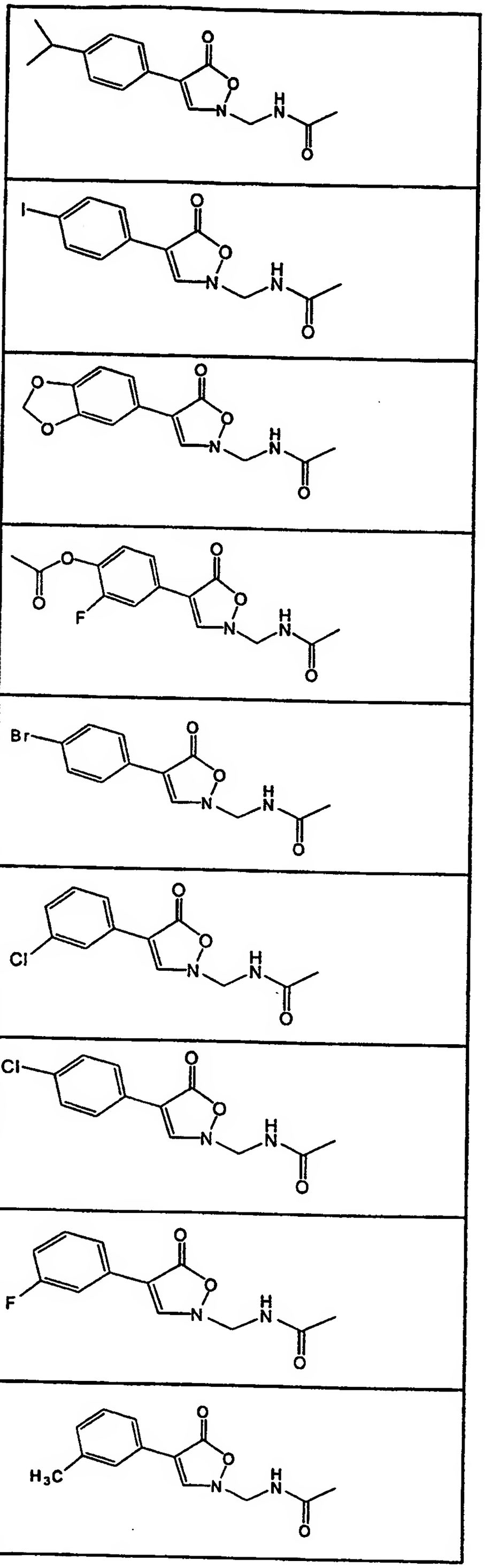


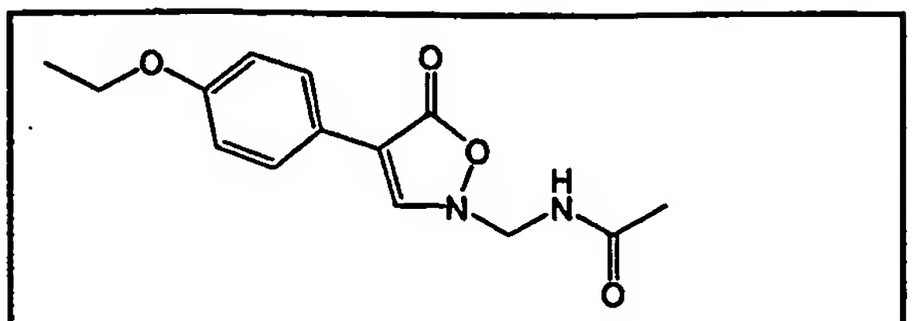


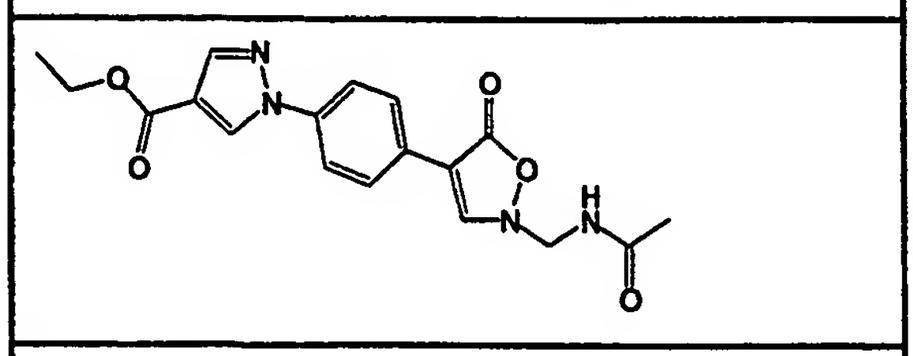


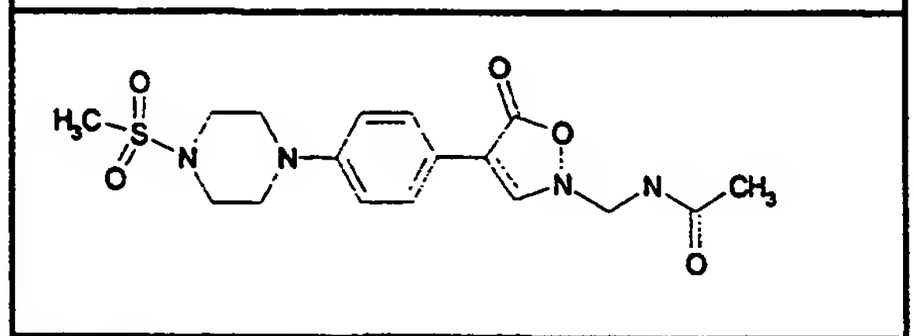


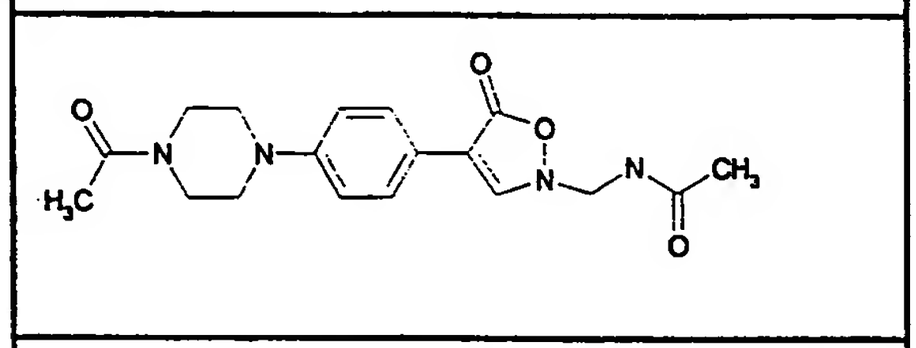


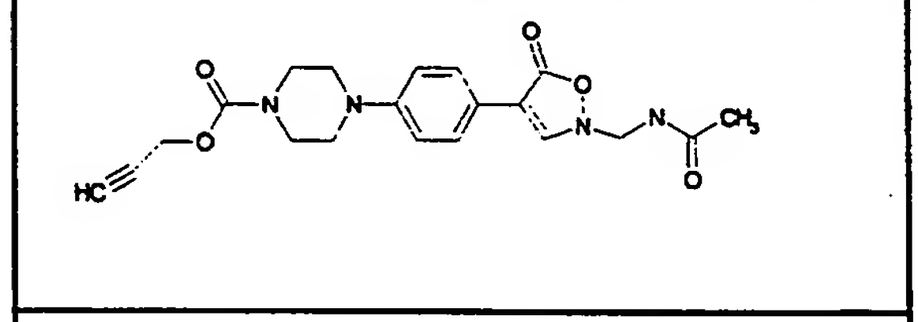


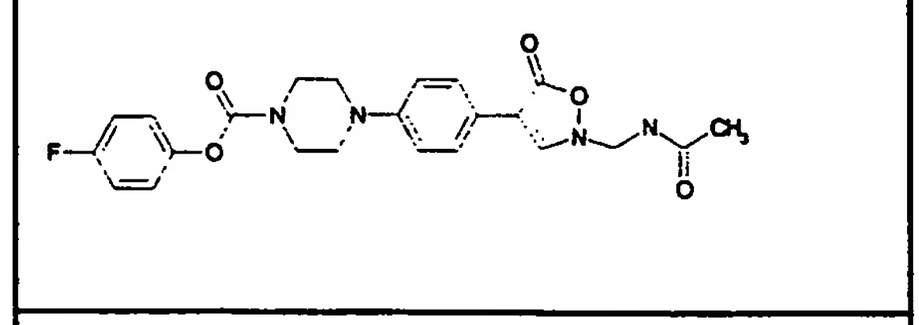


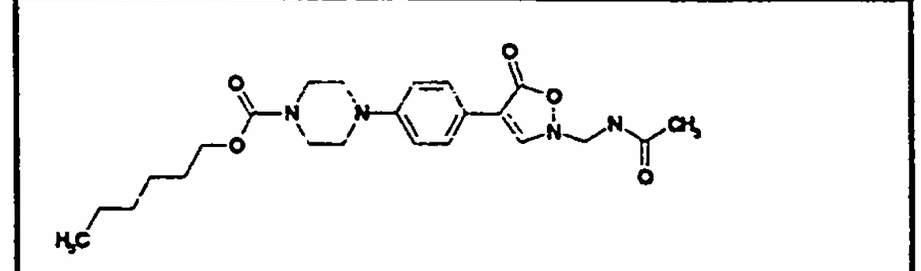


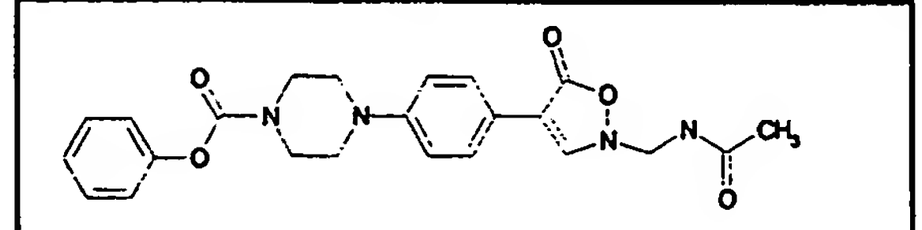


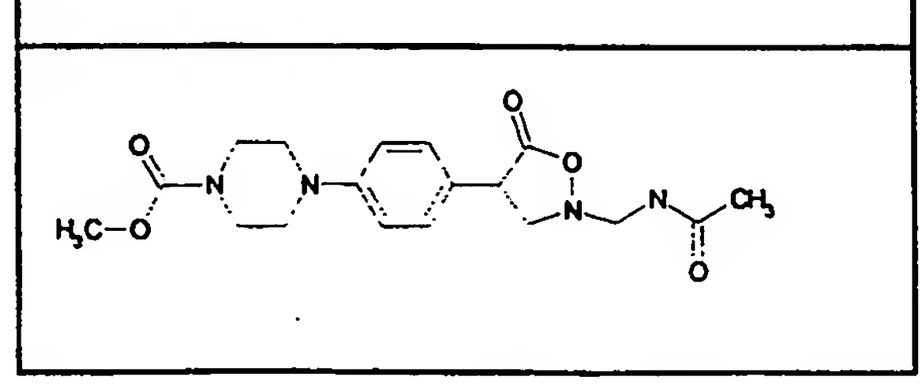


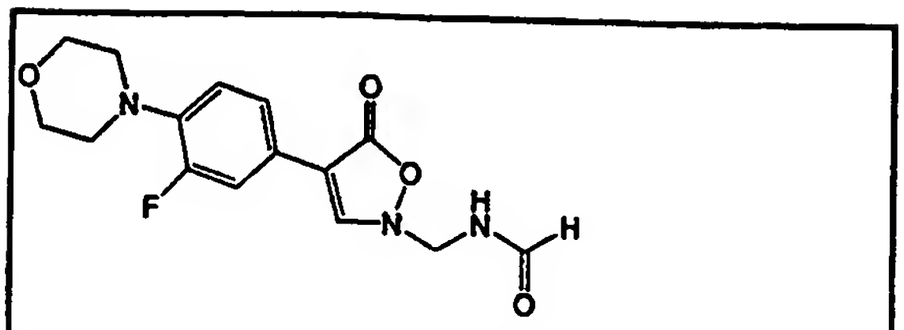


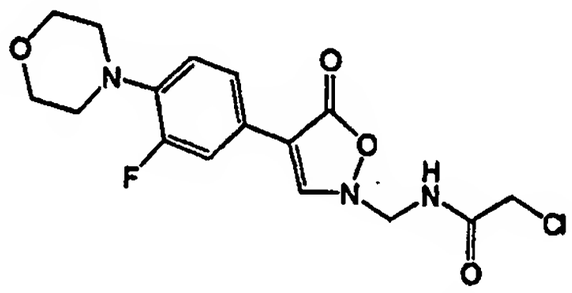


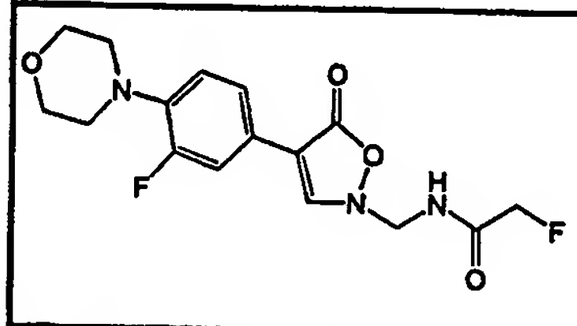


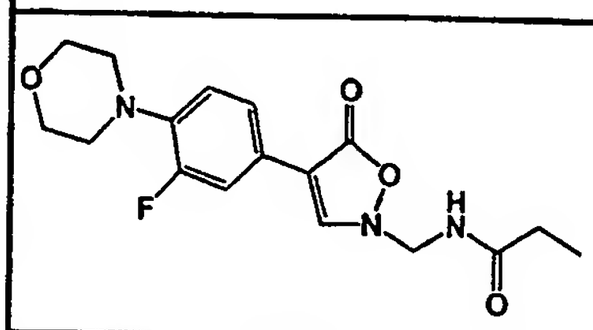


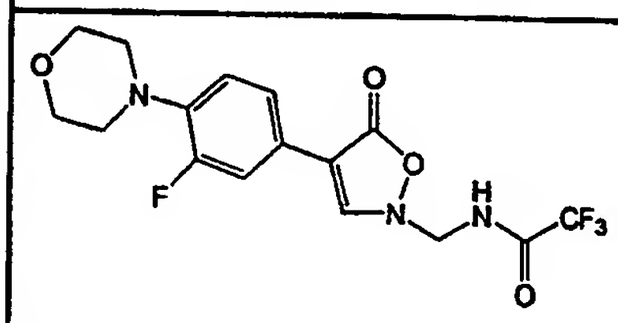


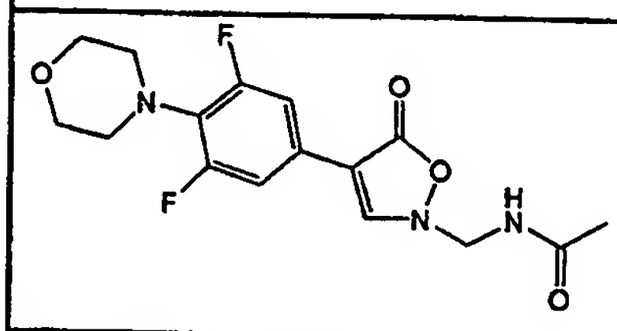


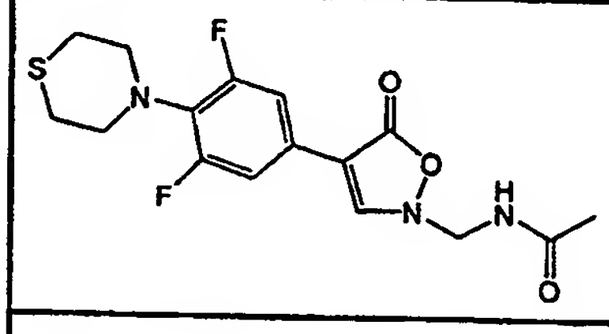


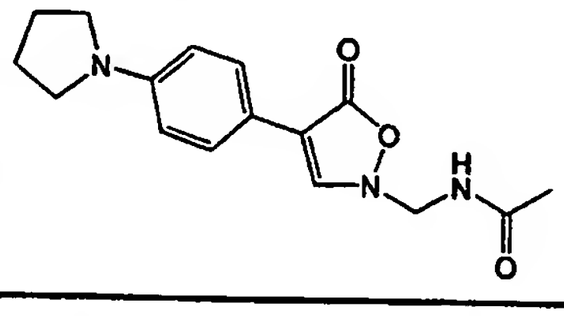


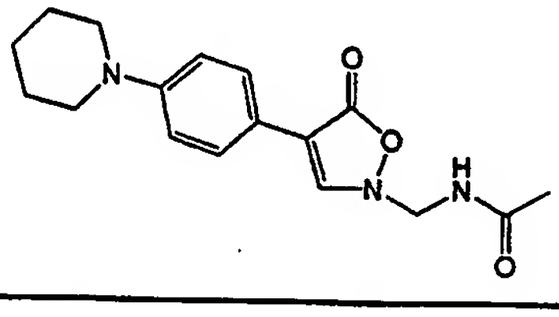


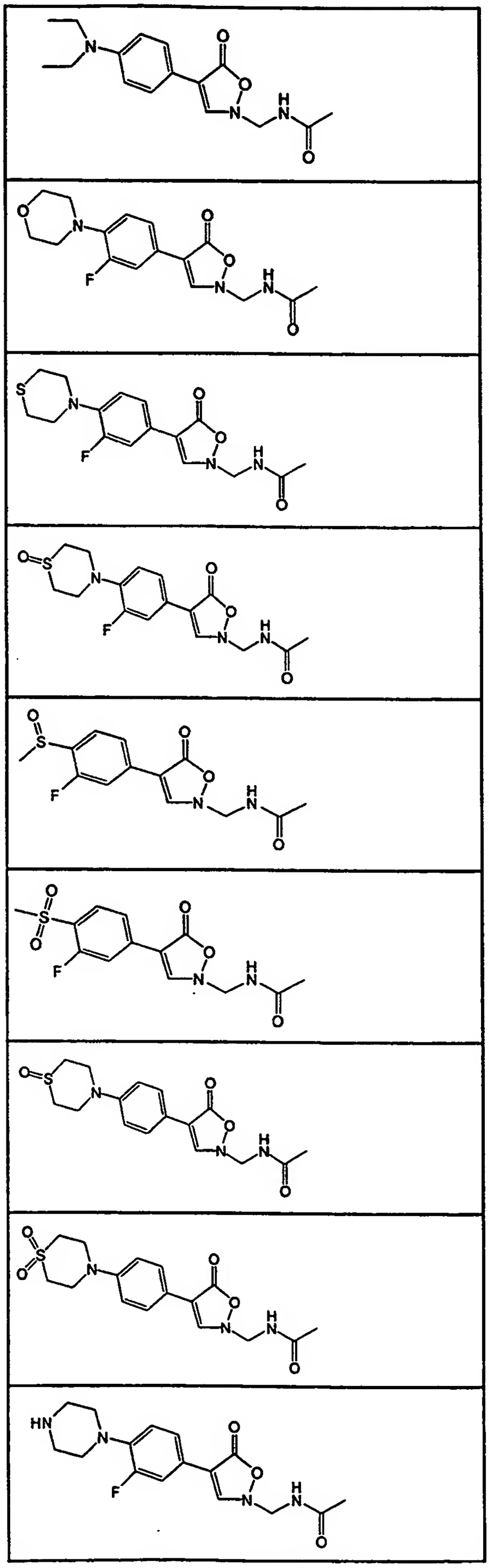


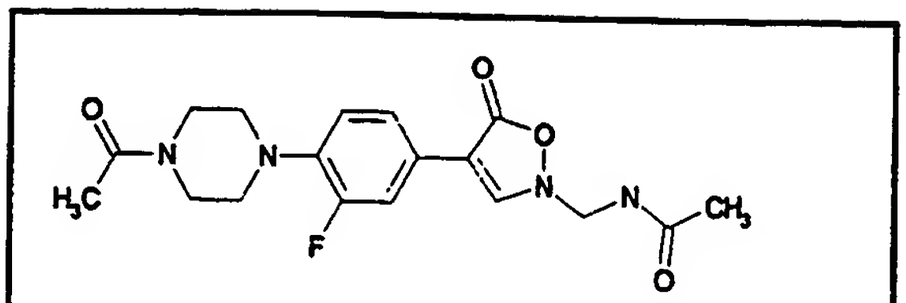


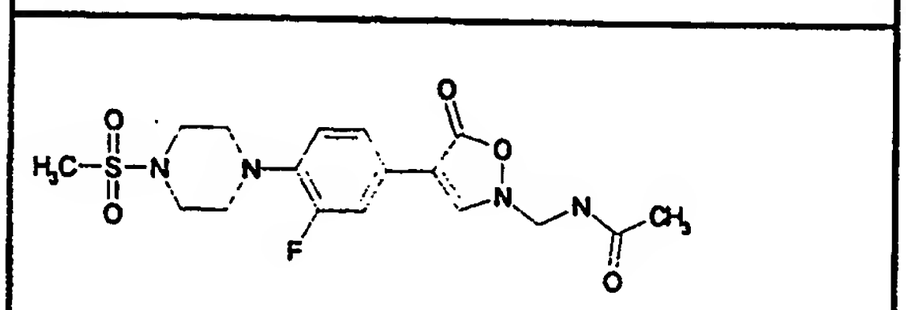


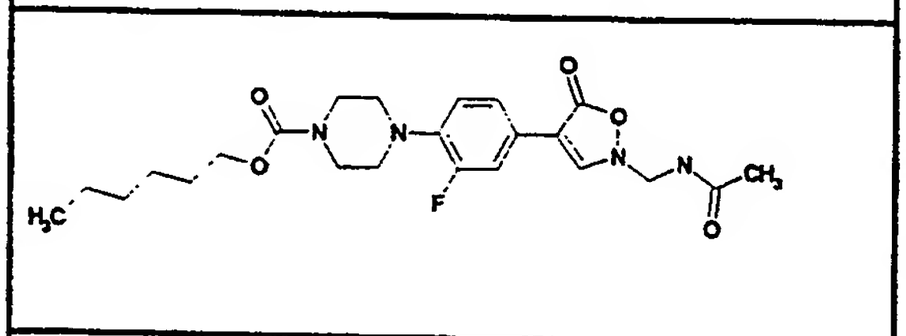


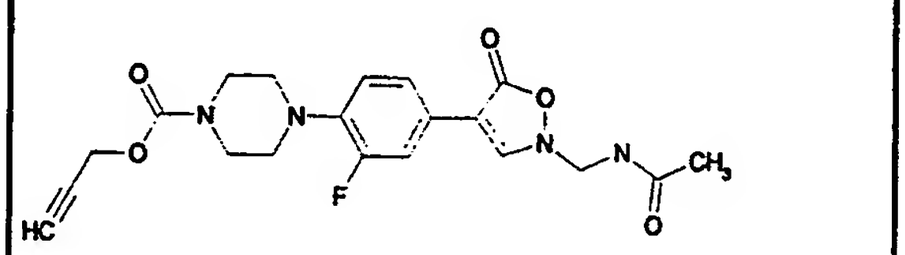


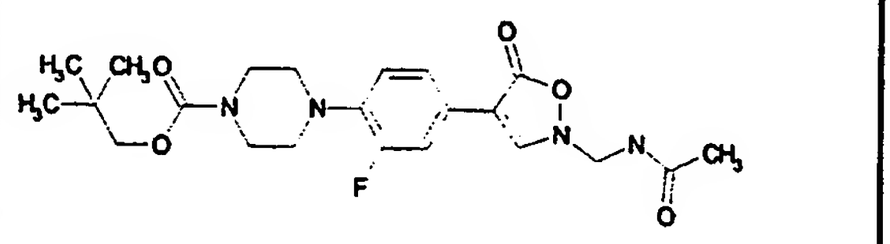


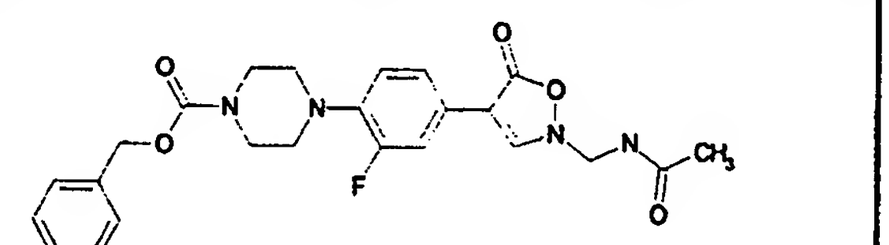


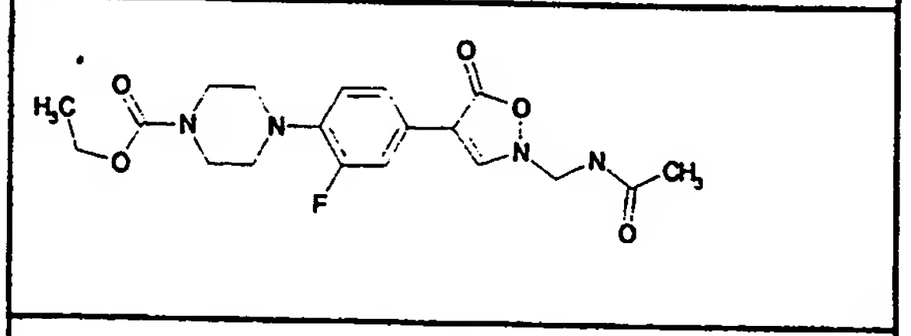


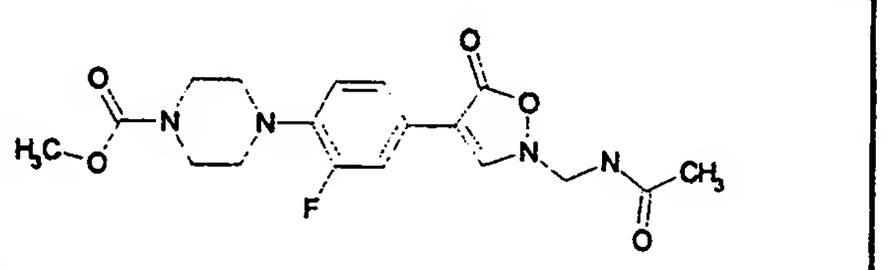


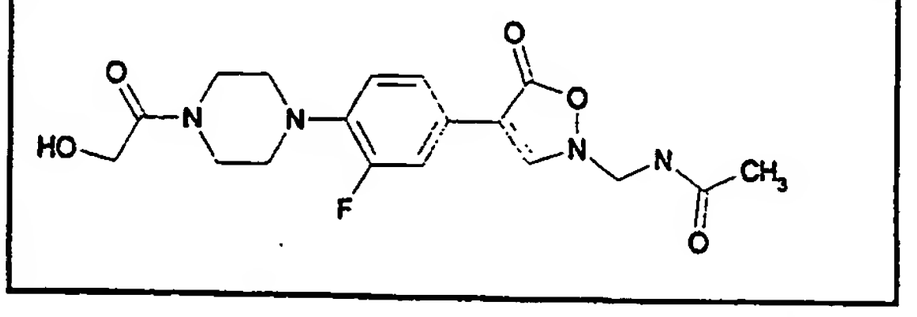


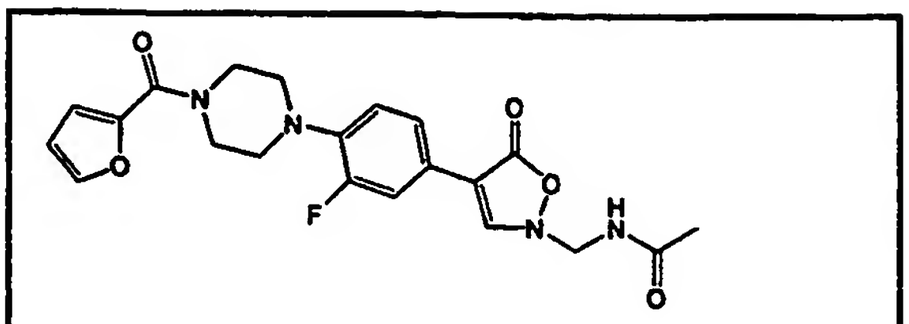


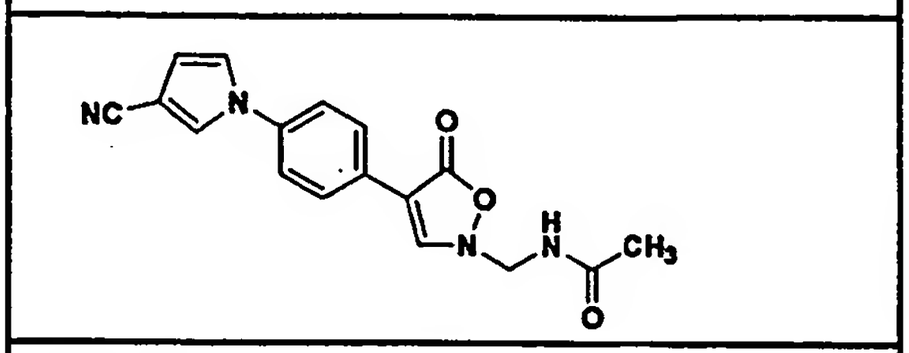


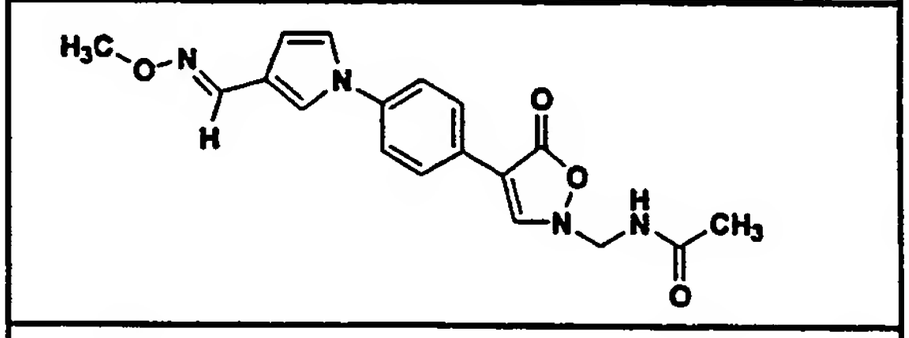


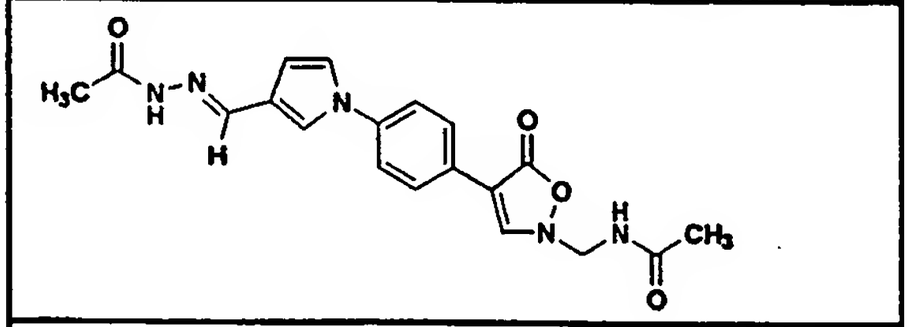


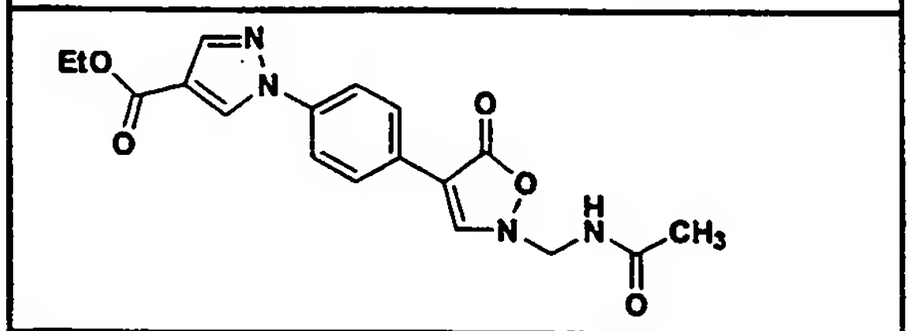


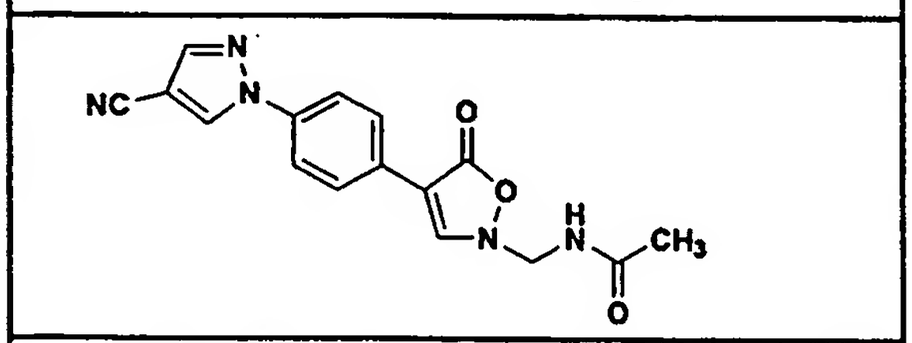


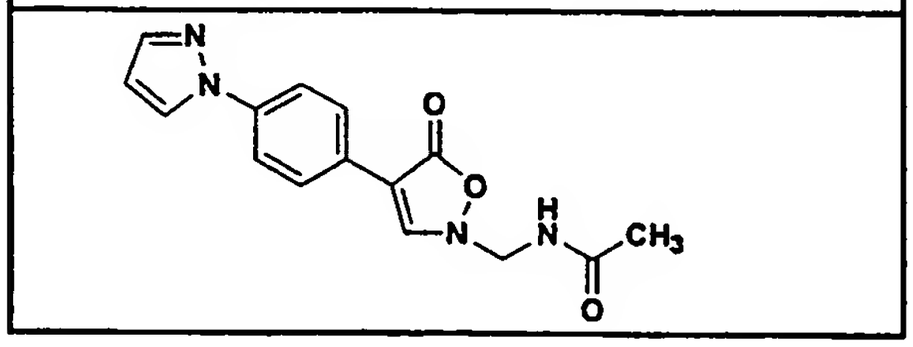










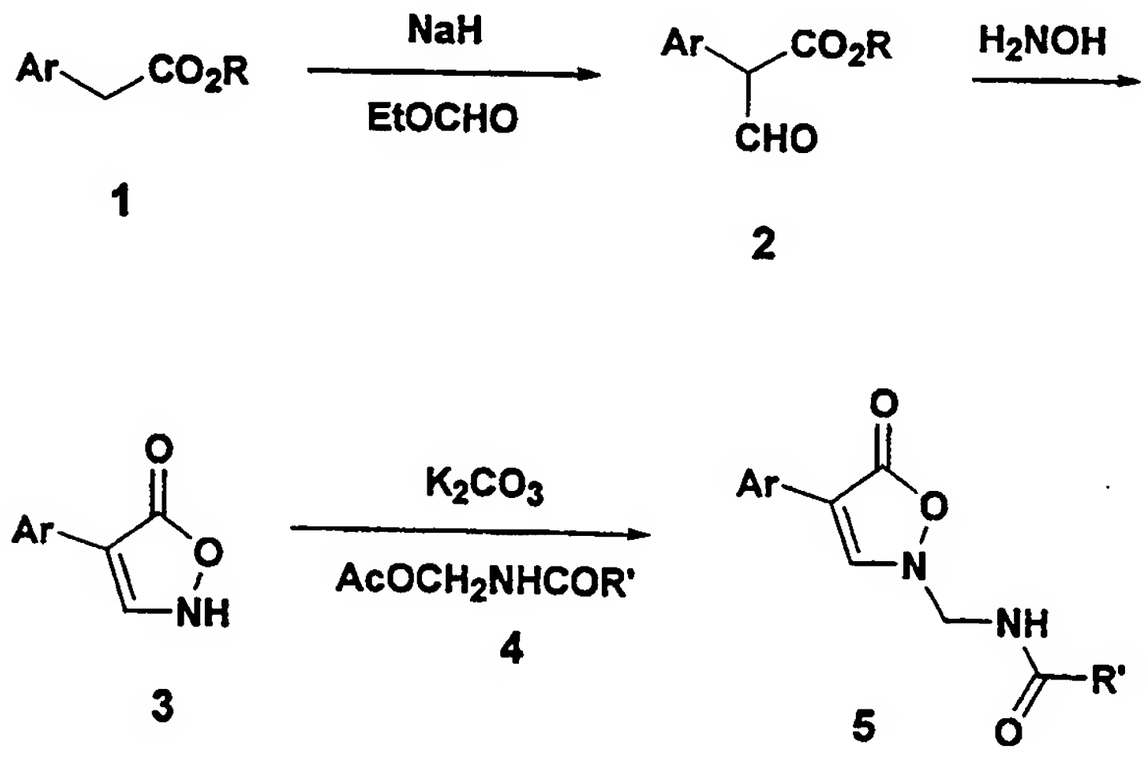


The compounds of the present invention can be made by the methods summarized below.

It will be apparent to those skilled in the art that the procedures described herein are representative in nature and that alternative procedures are feasible.

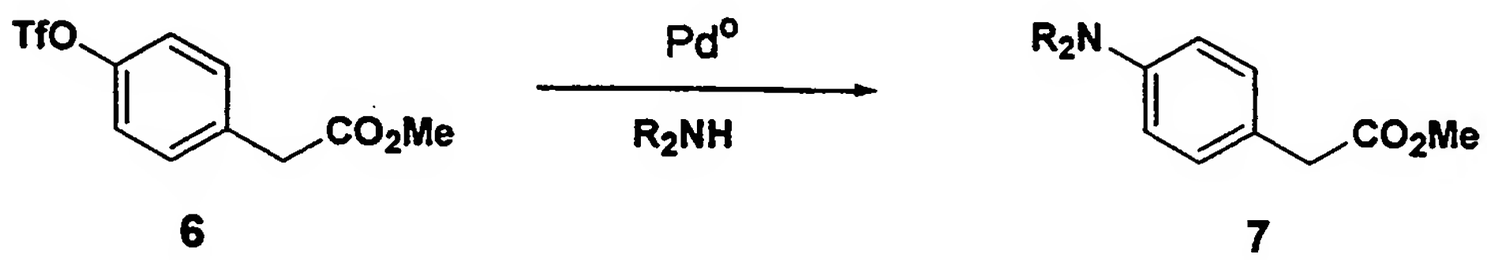
Isoxazolinones **5** of the present invention are preferably prepared via the sequence outlined in Scheme 1. Aryl acetic acids **1** are either commercially available or prepared by one of many well known methods in the chemical literature including but not limited to the sequence shown in Scheme 2 or 3. Isoxazolinone **3** is prepared by methods described by Marchesini [J. Org. Chem. 1984, **49**, p. 4287-4290]. Reaction of **1** with sodium hydride and ethyl formate provides **2** which is in turn reacted with hydroxylamine yielding **3**. Treatment of **3** with mild base, preferably potassium carbonate, in an appropriate solvent, preferably dichloromethane or *N, N*-dimethylformamide followed by addition of **4** (prepared by methods described by Barnes et al in US Patent 5, 284, 863) provides isoxazolinone **5**.

Scheme 1



An alternative way to prepare aryl acetic esters **1** of the present invention is shown in Scheme 2. Treatment of triflate **6** (prepared from methyl 4-hydroxyphenyl acetate by methods known by those skilled in the art) with an *N, N*- dialkylamine in the manner described by Buchwald [Tet. Lett., 1997, **38**, p. 6363-6366] produces esters exemplified by **7**. Aryl-bromides, -iodides, and -chlorides are also suitable as replacements for triflate **6** in Scheme 2. The *N, N*- dialkylamines used in Scheme 2 are either commercially available or are synthesized by literature procedures. Literature preparations of many cyclic *N, N*- dialkylamines have been detailed by Gadwood (WO 97/10223) and others are well known to those skilled in the art.

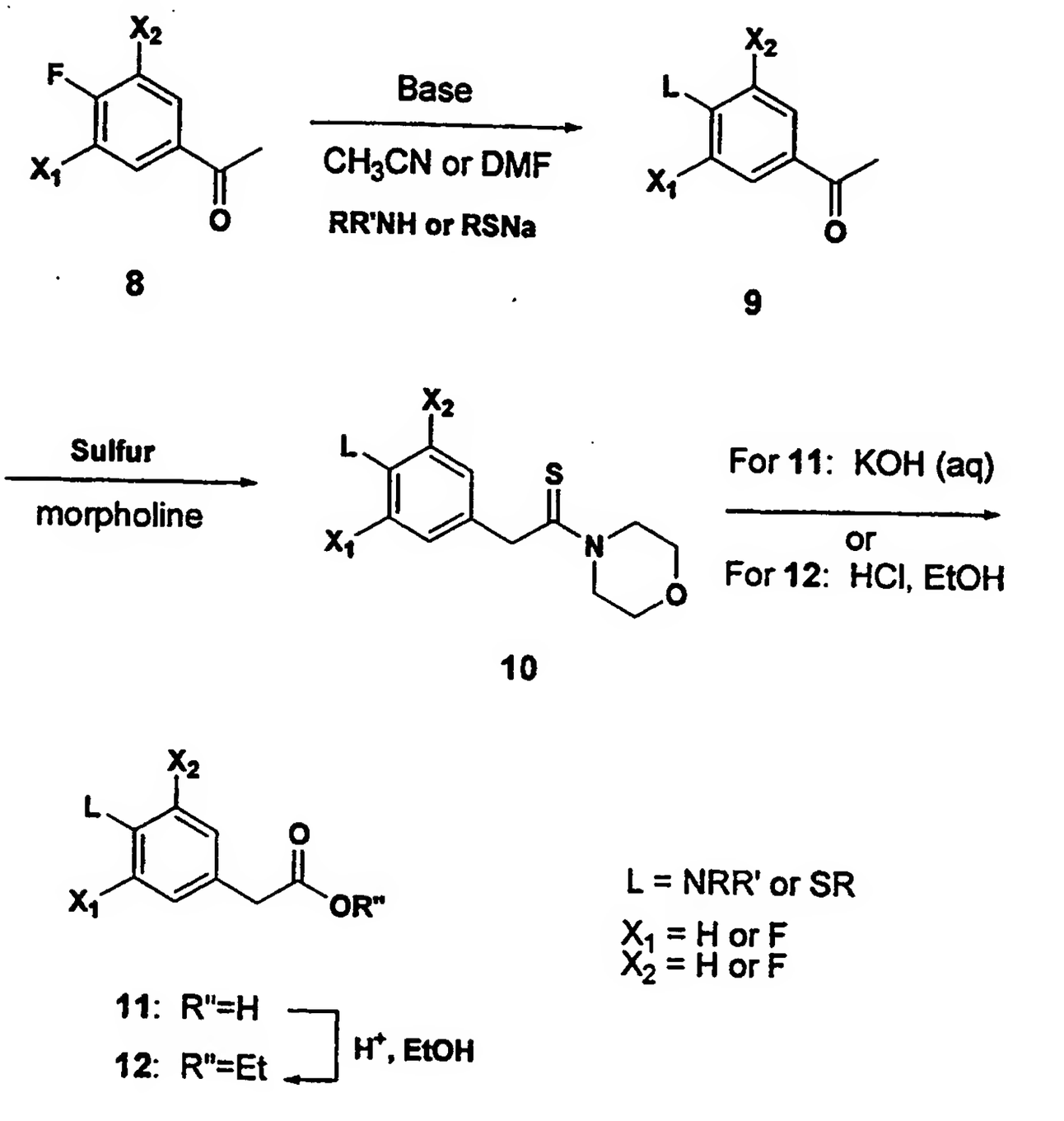
Scheme 2



6 **7**

Another alternative to prepare aryl acetic esters **1** of the present invention is shown in Scheme 3. Treatment of **8** with a mild base, preferably potassium carbonate, and a primary or secondary amine or thiolate, in a suitable solvent, preferably acetonitrile or *N, N*-dimethylformamide, at a temperature between 25°C and 100°C provides **9**. Compound **8** is commercially available. Compound **9** is converted to **11** or **12** by methods described by Gravestock (World Patent 97/14690). This sequence is also known to those skilled in the art as the Willgerodt reaction. Conversion of **11** to **12** can also be accomplished by various methods known in the chemical literature including but not limited to treatment with acid in hot alcohol.

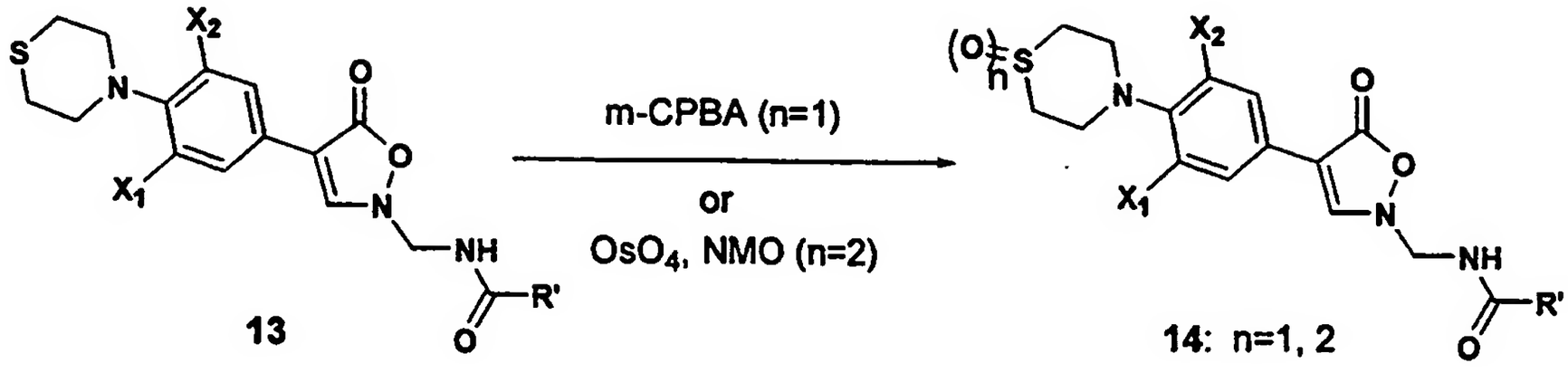
Scheme 3



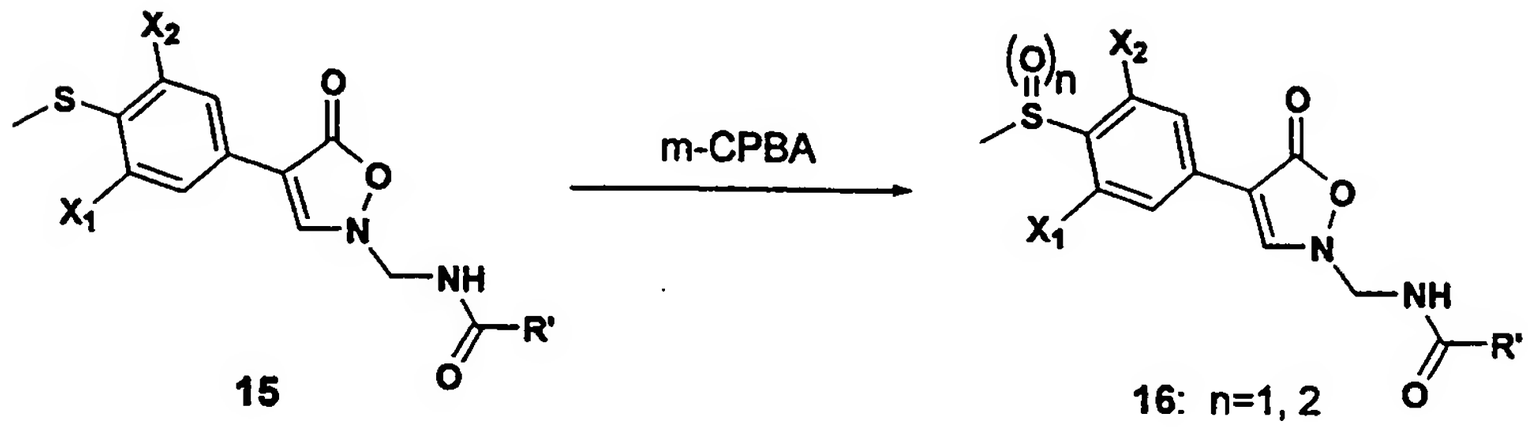
8 9 10

Sulfoxides and sulfones **14** and **16** are prepared by treating sulfides **13** and **15**, respectively with an oxidizing agent such as m-chloroperoxybenzoic acid or osmium tetroxide by methods known by those skilled in the art and exemplified by Barbachyn [J. Med. Chem., 1996, **39**, 680-685].

Scheme 4

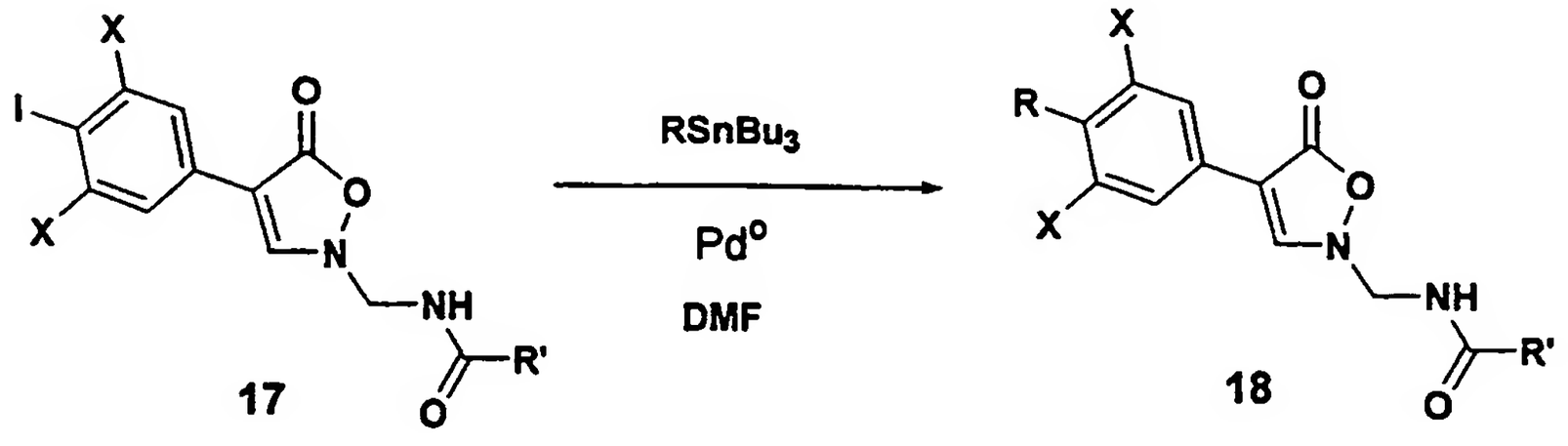


X_1 = H or F
X_2 = H or F



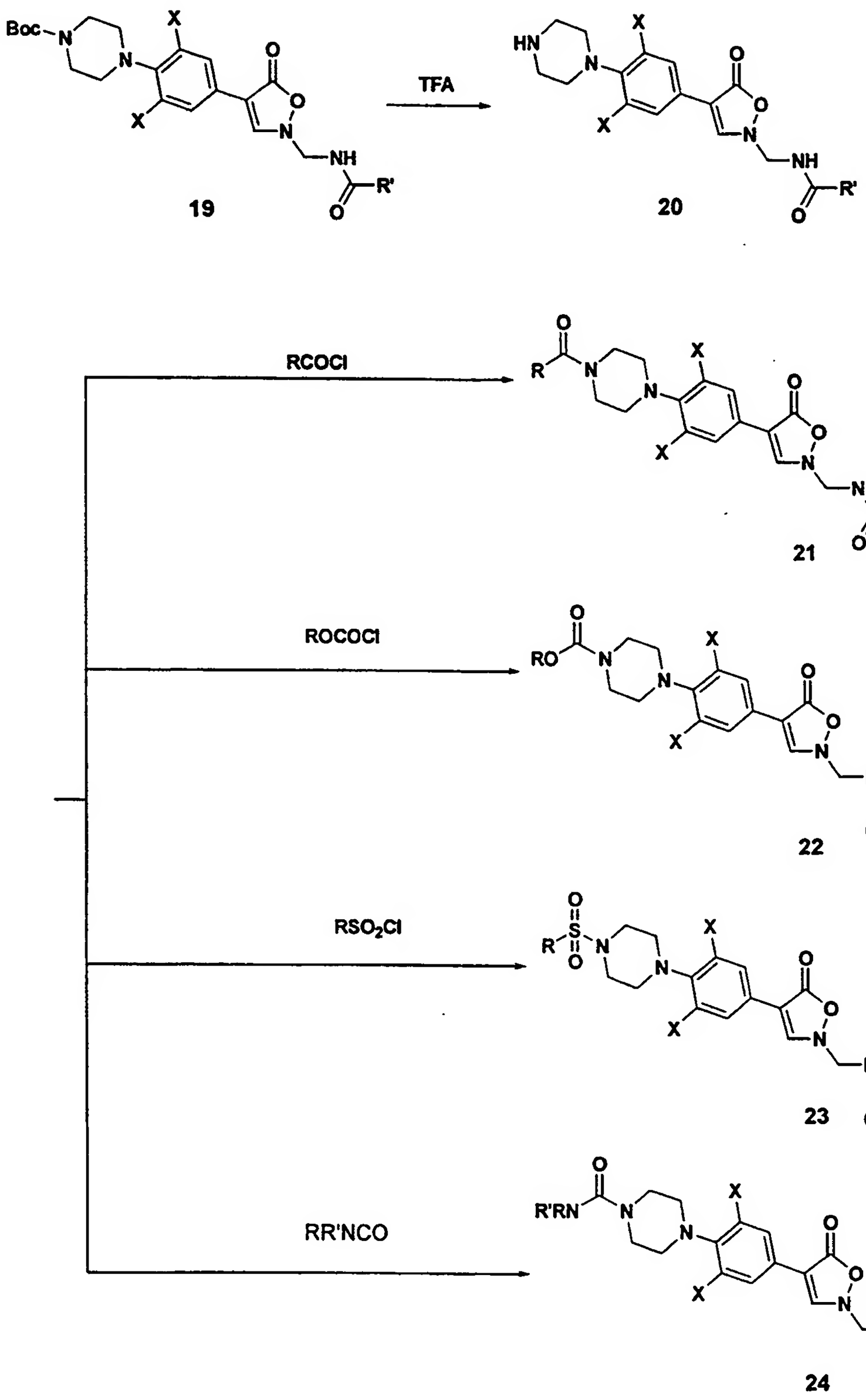
An alternative method of preparing compound **18** of the present invention is shown in Scheme 5. Treatment of **17** with an appropriate organostannane provides **18**. This method is known by those skilled in the art as the Stille cross-coupling reaction.

Scheme 5



Preparation of **21**, **22**, **23**, and **24** of the present invention is described in Scheme 6. Treatment of **19** with trifluoroacetic acid provides **20**. Compound **20** is treated with an acid chloride, chloroformate, sulfonyl halide, or isocyanate in the presence of triethylamine by methods well known in the chemical literature to provide **21**, **22**, **23**, and **24**, respectively.

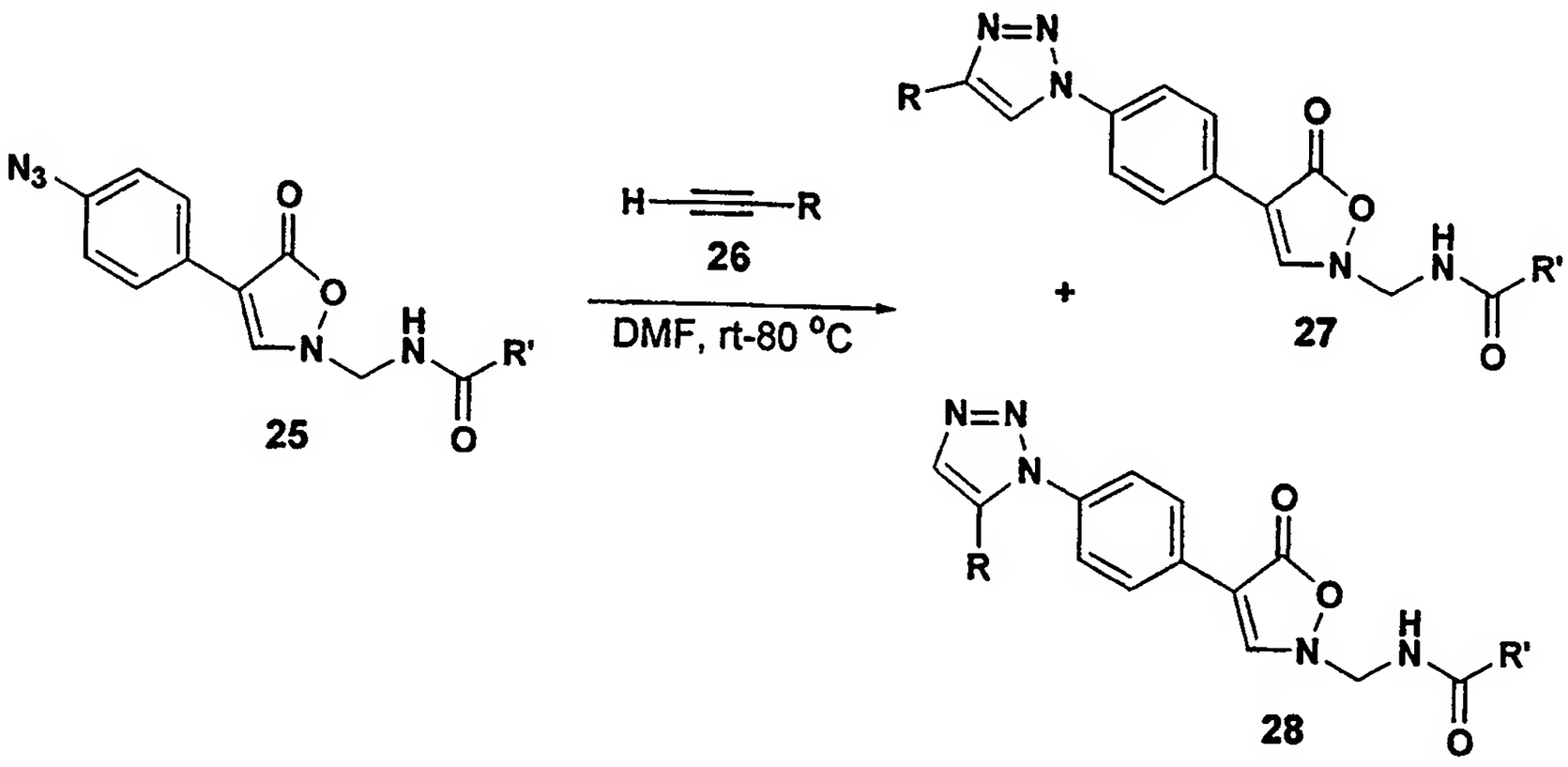
Scheme 6



The triazole-substituted compounds **27** and **28** are prepared by cyclization of the azide **25** with acetylenes **26** (Scheme 7). This is a

standard 3+2 cycloaddition which is well documented in the chemical literature. The acetylenes **26** are either commercially available or prepared by literature procedures. For example, cyanoacetylene is prepared according to Murahashi [J.Chem. Soc. Jap., 1956, **77**, 1689]. The cyclization reaction was usually carried out in a suitable solvent such as DMF, at a temperature between 25°C and 80°C. Other suitable solvents include but are not limited to DMSO, NMP, and DMA. The two cyclization adducts **27** and **28** were separated using preparative HPLC or by triturating with a suitable solvent such as ethyl acetate. Other suitable solvents for trituration include but are not limited to methanol, ethanol, diethyl ether, and acetone.

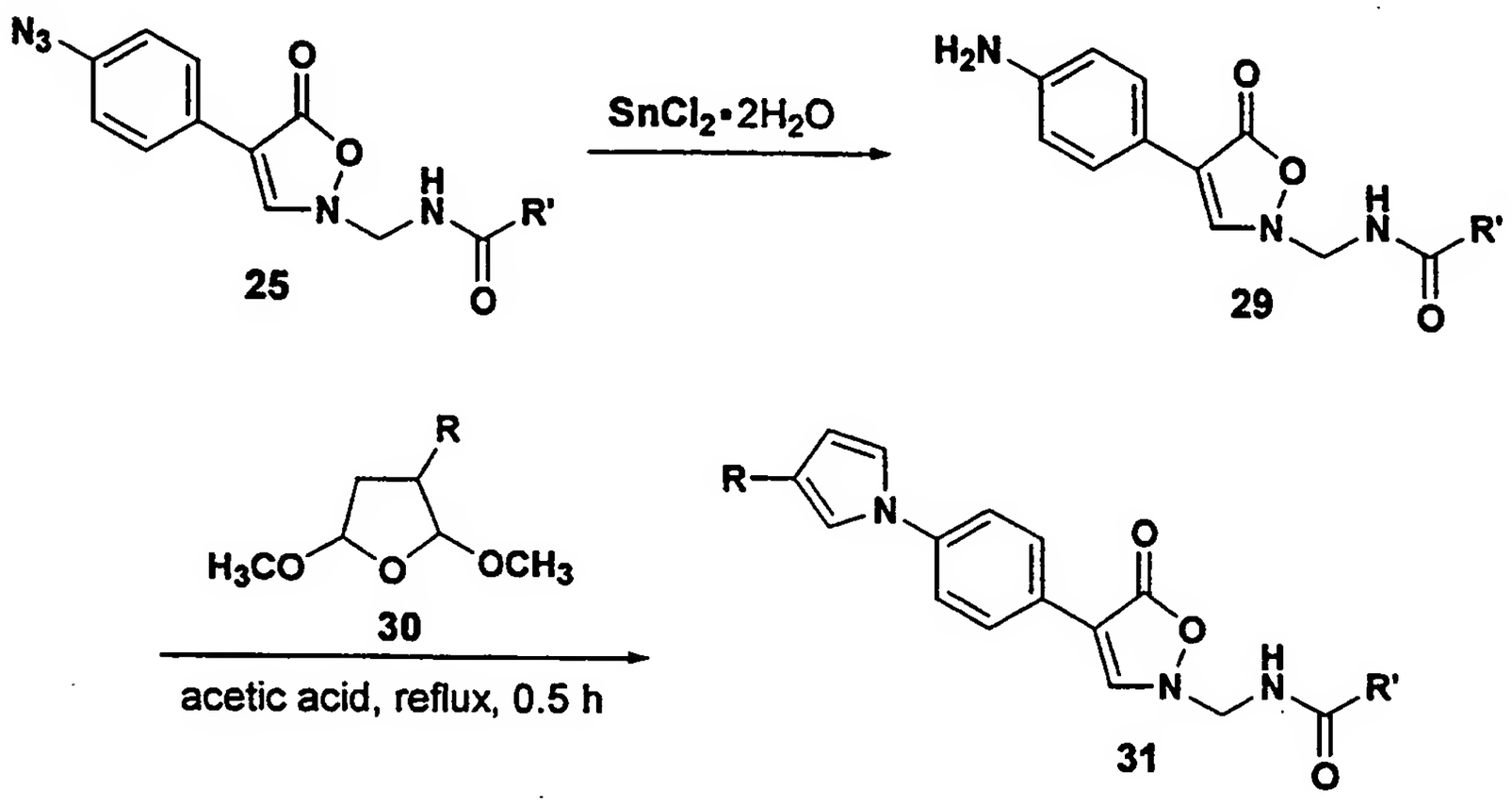
Scheme 7: 1,2,3-Triazoles



The azidophenylisoxazolinone **25** is reduced to aminophenylisoxazolinone **29** via one of the many well known methods in the chemical literature including but not limited to the treatment with stannous chloride in a suitable solvent such as a 2:1 combination of ethyl acetate and methanol . Treatment of aminophenylisoxazolinones **29** with 2,5-dimethoxytetrahydrofurans **30** in acetic acid provide pyrrole-substituted isoxazolinones **31** (Scheme 8). Subsequent conversions of

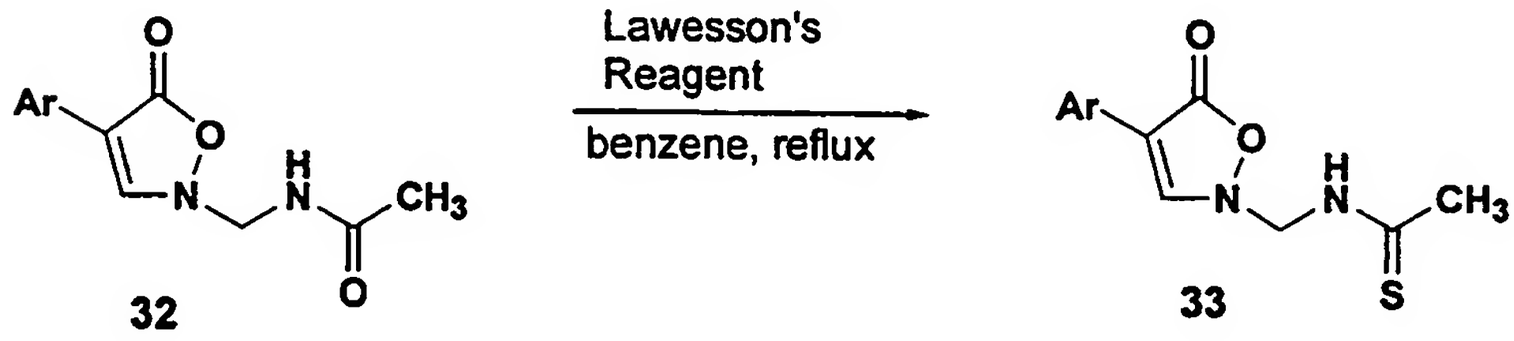
the pyrrole (R = CHO) are also possible, for instance the corresponding oxime can be prepared by refluxing with 50 % aqueous hydroxylamine in methanol.

Scheme 8: Pyrroles



N-thioacetates **33** may be prepared from the corresponding N-acetates **32** using a variety of well known literature methods, for instance by refluxing in benzene with Lawesson's reagent. Other solvents such as toluene and xylene are also suitable.

Scheme 9: Thioacetates



It will be understood that where the substituent groups used in the above reactions contain certain reaction-sensitive functional groups which

might result in undesirable side-reactions, such groups may be protected by conventional protecting groups known to those skilled in the art. Suitable protecting groups and methods for their removal are illustrated, for example, in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, 1991). It is intended that such "protected" intermediates and end-products are included within the scope of the present disclosure and claims.

Some of the desired end-products of formula I contain an amine. In these cases, the final product may be recovered in the form of a pharmaceutically acceptable acid addition salt, e.g. by addition of the appropriate acid such as HCl, HI or methane-sulfonic acid to the amine.

It will be appreciated that certain products within the scope of formula I may have substituent groups which can result in formation of optical isomers. It is intended that the present invention include within its scope all such optical isomers as well as epimeric mixtures thereof, i.e. R- or S- or racemic forms.

The compounds of the invention are useful because they possess pharmacological activities in animals, including particularly mammals and most particularly, humans. The novel isoxazolinone derivatives of general formula I , or pharmaceutically acceptable salts or prodrugs thereof, are potent antibiotics active against gram-positive bacteria. While they may be used, for example, as animal feed additives for promotion of growth, as preservatives for food, as bactericides in industrial applications, for example in waterbased paint and in the white water of paper mills to inhibit the growth of harmful bacteria, and as disinfectants for destroying or inhibiting the growth of harmful bacteria on medical and dental equipment, they are especially useful in the treatment

of bacterial infections in humans and other animals caused by the gram-positive bacteria sensitive to the new derivatives.

The pharmaceutically active compounds of this invention may be used alone or formulated as pharmaceutical compositions comprising, in addition to the active isoxazolinone ingredient, a pharmaceutically acceptable carrier or diluent. The compounds may be administered by a variety of means, for example, orally, topically or parenterally (intravenous or intramuscular injection). The pharmaceutical compositions may be in solid form such as capsules, tablets, powders, etc. or in liquid form such as solutions, suspensions or emulsions. Compositions for injection may be prepared in unit dose form in ampules or in multidose containers and may contain additives such as suspending, stabilizing and dispersing agents. The compositions may be in ready-to-use form or in powder form for reconstitution at the time of delivery with a suitable vehicle such as sterile water.

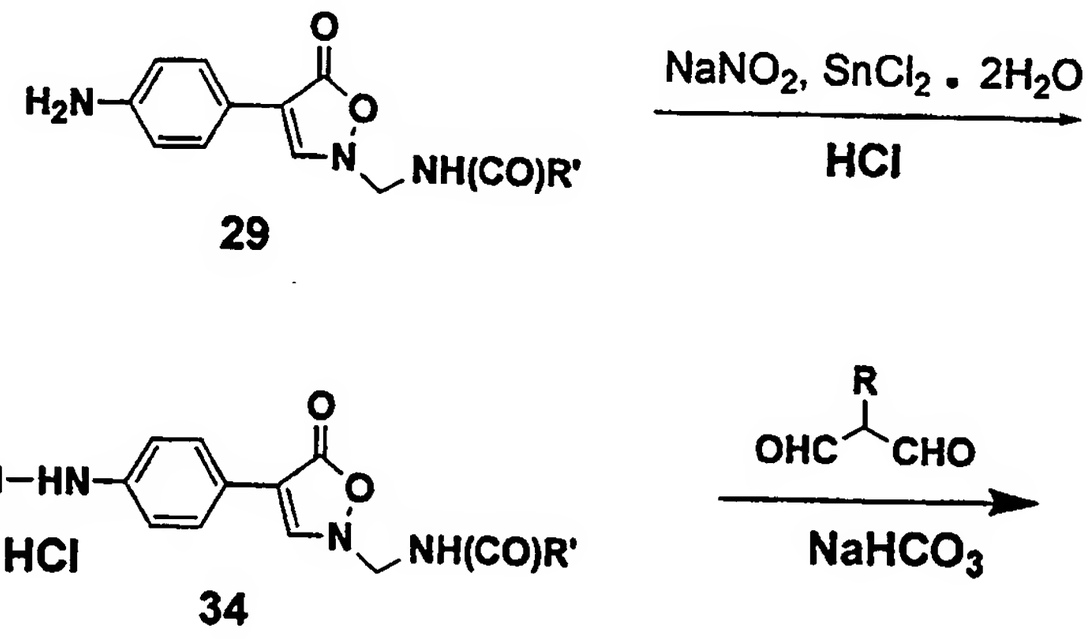
Thus, according to another aspect of the invention, there is provided a method of treating a bacterial infection which comprises administering a therapeutically effective amount of the compound to a host, particularly a mammalian host and most particularly a human patient. The use of the compounds of the present invention as pharmaceuticals and the use of the compounds of the invention in the manufacture of a medicament for the treatment of bacterial infections are also provided.

The dosage to be administered depends, to a large extent, on the particular compound being used, the particular composition formulated, the route of administration, the nature and condition of the host and the particular situs and organism being treated. Selection of the particular preferred dosage and route of application, then, is left to the discretion of

the physician or veterinarian. In general, however, the compounds may be administered parenterally or orally to mammalian hosts in an amount of from about 25 mg/day to about 2 g/day.

The preparations of pyrazoles substituted compounds are outlined in Scheme 10. Compound **29** was diazotized and then reduced to form hydrazine hydrochloride salt **34** via one of the many well known methods in the chemical literature including but not limited to the treatment with sodium nitrite and stannous chloride. Treatment of **34** with ethoxycarbonylmalondiadehyde, cyanomalondiadehyde [prepared according to Bertz, S.H., Dabbagh, G. and Cotte, P. in J. Org. Chem, 1982, **47**, p. 2216,] or malondiadehyde [prepared according to Martinez,A.M., Cushmac, G.E., Rocek, J. in J. Amer. Chem. Soc, 1975, **97**, p. 6502] in the presence of sodium bicarbonate at room temperature provides compound **35.**

Scheme 10: Pyrazoles



In Vitro Activity

Samples of the compounds prepared below in Examples 1 - 97 after solution in water and dilution with Nutrient Broth were found to exhibit the following ranges of Minimum Inhibitory Concentrations (MIC) versus the indicated microorganisms as determined by tube dilution. The MICs were determined using a broth micro dilution assay in accordance with that recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Mueller-Hinton medium was used except for Streptococci which was tested in Todd Hewitt broth. The final bacterial inoculate contained approximately 5×10^5 cfu/ml and the plates were incubated at 35°C for 18 hours in ambient air (Streptococci in 5% CO_2). The MIC was defined as the lowest drug concentration that prevented visible growth.

Microorganism	MIC value in ug/ml
S. pneumoniae A9585	≤ 8
E. faecalis A20688	≤ 16
S. aureus A15090, penicillinase positive	≤ 16

ILLUSTRATIVE EXAMPLES

The following examples illustrate the invention, but are not intended as a limitation thereof. The abbreviations used in the examples are conventional abbreviations well-known to those skilled in the art. Some of the abbreviations used are as follows:

h	=	hour(s)
mol	=	mole(s)
mmol	=	mmole(s)
g	=	gram(s)
min	=	minute(s)
rt	=	room temperature
THF	=	tetrahydrofuran
L	=	liter(s)
mL	=	milliliter(s)
Et_2O	=	diethyl ether
EtOAc	=	ethyl acetate
MeOH	=	methanol
DMF	=	dimethylformamide

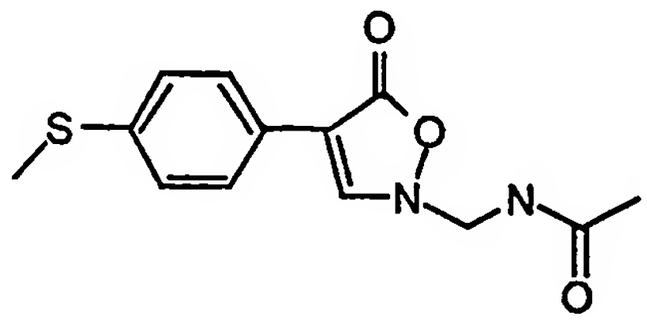
In the following examples, all temperatures are given in degrees Centigrade. Melting points were determined on an electrothermal apparatus and are not corrected. Proton and carbon-13 nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker AM-300 or a Varian Gemini 300 spectrometer. All spectra were determined in $CDCl_3$, DMSO-d_6, CD_3OD, or D_2O unless otherwise indicated. Chemical shifts are reported in δ units relative to tetramethylsilane (TMS) or a reference solvent peak and interproton coupling constants are reported in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; dd, doublet of doublets; dt, doublet of triplets; and app d, apparent doublet, etc. Infrared spectra were determined on a Perkin-Elmer 1800 FT-IR spectrometer from 4000 cm^{-1} to 400 cm^{-1}, calibrated to 1601 cm^{-1} absorption of a polystyrene film, and are reported in reciprocal centimeters (cm^{-1}). Mass spectra were recorded on a Kratos MS-50 or a Finnegan 4500 instrument utilizing direct chemical ionization (DCI, isobutene), fast atom

bombardment (FAB), or electron ion spray (ESI). Ultraviolet spectra were determined on a Hewlett Packard 8452 diode array spectrophotometer in the solvent indicated.

Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel plates (60F-254) and visualized using UV light, iodine vapors, and/or staining by heating with methanolic phosphomolybdic acid. Column chromatography, also referred to as flash chromatography, was performed in a glass column using finely divided silica gel at pressures somewhat above atmospheric pressure with the indicated solvents. Reversed-phase analytical thin-layer chromatography was carried out on precoated reverse phase plates and visualized using UV light or iodine vapors.

EXAMPLE 1

N-[[4-(4-methylthiophenyl)-5-oxo-2-isoxazolinyl]methyl]acetamide



A. Ethyl 4-methylthiophenylacetate

To a solution of 4-methylthiophenylacetic acid (1.0 g, 5.48 mmol) in 55 mL of ethanol was slowly added a catalytic amount of concentrated sulfuric acid. The mixture was stirred at room temperature overnight and then concentrated at reduced pressure. The residue was partitioned between methylene chloride and sodium bicarbonate. The organic layer was washed with brine, dried with magnesium sulfate, filtered, and concentrated to yield 1.1 g of a colorless oil (96%). ^{1}H NMR (300MHz,

$CDCl_3$) δ 7.22 (s, 4 H), 4.15 (q, J=6 Hz, 2 H), 3.57 (s, 2 H), 2.47 (s, 3 H), 1.25 (t, J=6 Hz, 3 H).

B. Ethyl 4-methylthio-α-formyl-phenylacetate

A suspension of NaH (0.84 g, 20.8 mmol) was added at room temperature to a solution of ethyl 4-methylthiophenylacetate (1.1 g, 5.2 mmol) in ethyl formate (20 mL). The mixture was stirred at room temperature for 1 hour and then cold 0.5 N HCl (20 mL) was added slowly. The crude reaction was then extracted with ether, and the organic layer was washed with sodium bicarbonate, brine, dried over magnesium sulfate, filtered, and concentrated to yield 1.2 g of ethyl 4-methylthio-α-formyl-phenylacetate as a colorless oil, which was used in the next step without purification.

C. 4-(4-methylthio)-phenylisoxazolin-5-one

To a solution of ethyl 4-methylthio-α-formyl-phenylacetate in 20 mL of methanol and 1 mL of water was added hydroxylamine hydrochloride (0.54 g, 7.8 mmol). The mixture was heated to reflux for 1 hour. The solvent was evaporated and the residue was triturated with water to afford a precipitate, which was then further triturated with ether to yield 0.48 g (two steps, 44%) of a pale yellow solid. ^{1}H NMR (300MHz, MeOH-d_4) δ 8.74 (s, 1 H), 7.66 (d, J=8 Hz, 2 H), 7.25 (d, J=8 Hz, 2 H), 2.46 (s, 3 H).

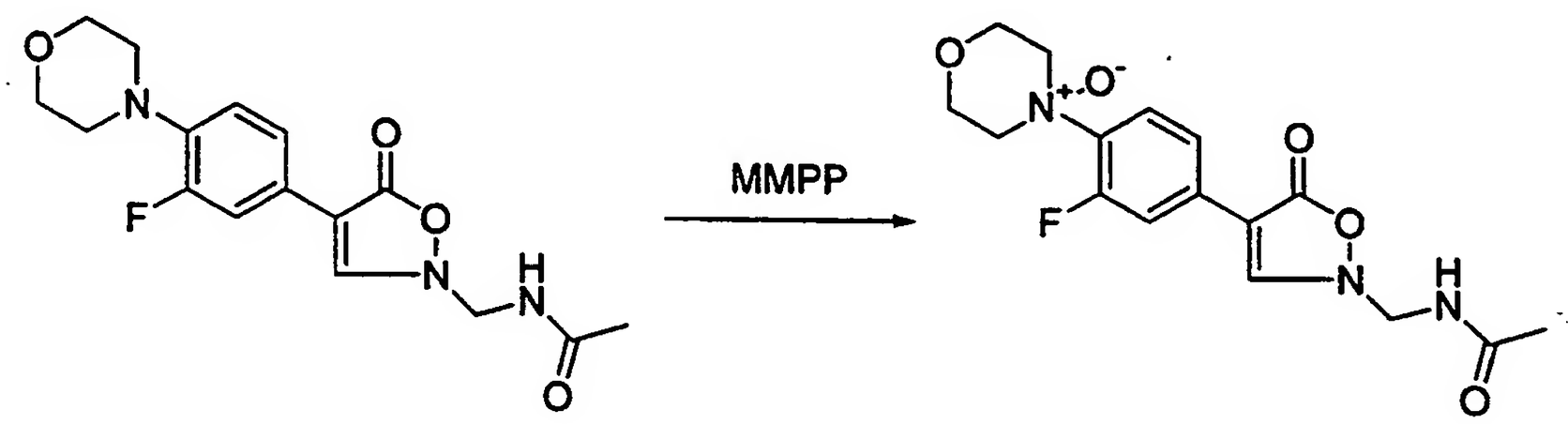
D. N-[[4-(4-methylthiophenyl)-5-oxo-2-isoxazolinyl]methyl]acetamide

To a solution of 4-(4-methylthio)-phenylisoxazolin-5-one (0.2 g, 0.97 mmol) in 10 mL of methylene chloride was added potassium carbonate (0.67 g, 4.85 mmol) and N-(hydroxymethyl) acetamide acetate (0.64 g, 4.85 mmol). The mixture was stirred at room temperature for 18 hours. It was then poured into 10 mL of 1N HCl and extracted three times with chloroform. The organic layer was then washed with sodium

bicarbonate, brine, dried over magnesium sulfate, filtered, concentrated to yield a tan solid, which was then recrystallized with hexane/chloroform. The resulting solid was further purified by triturating with ether to yield 0.186 g (69%) of a tan solid. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.93 (s, 1 H), 7.72 (d, J=9 Hz, 2 H), 7.28 (d, J=9 Hz, 2 H), 5.02 (d, J=6 Hz, 2 H), 2.48 (s, 3 H), 1.84 (s, 3 H).

EXAMPLE 2

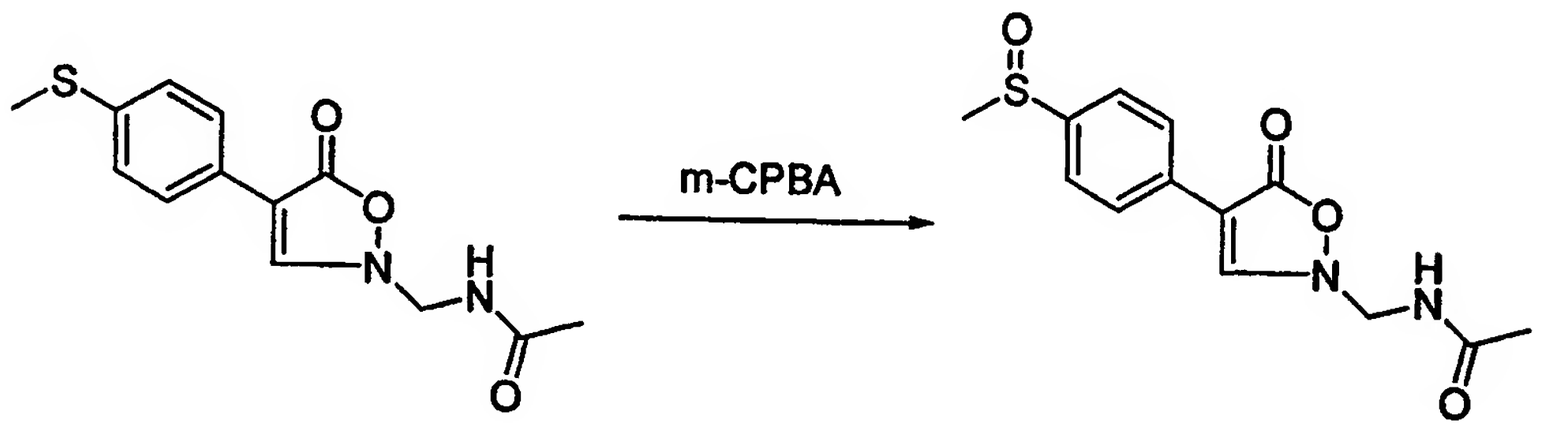
N-{[4-(3-fluoro-4-oxido-4-morpholin-4-ylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide



To N-{[4-(3-fluoro-4-morpholin-4-ylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (200 mg, 0.60 mmol) in 50 mL methanol was added magnesium monoperoxyphthalate (300 mg, 0.60 mmol). After 2 hours at ambient temperature the white precipitate was filtered and the filtrate was concentrated. The remaining residue was pushed through a plug of basic alumina with dichloromethane. The eluant was concentrated and recrystallized from dichloromethane / hexanes to afford 162 mg (44%) of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 9.19 (s, 1H), 9.02 (t, *J* = 6.1 Hz, 1H), 8.62-8.55 (m, 2H), 7.82-7.75 (m, 2H), 5.09 (d, *J* = 6.0 Hz, 2H), 4.44 (app t, *J* = 11.1 Hz, 2H), 4.08 (app t, *J* = 9.6 Hz, 2H), 3.78 (app d, *J* = 11.1 Hz, 2H), 2.89 (app d, *J* = 10.5 Hz, 2H), 1.86 (s, 3H); ESI $(M+H)^+$=352.

EXAMPLE 3

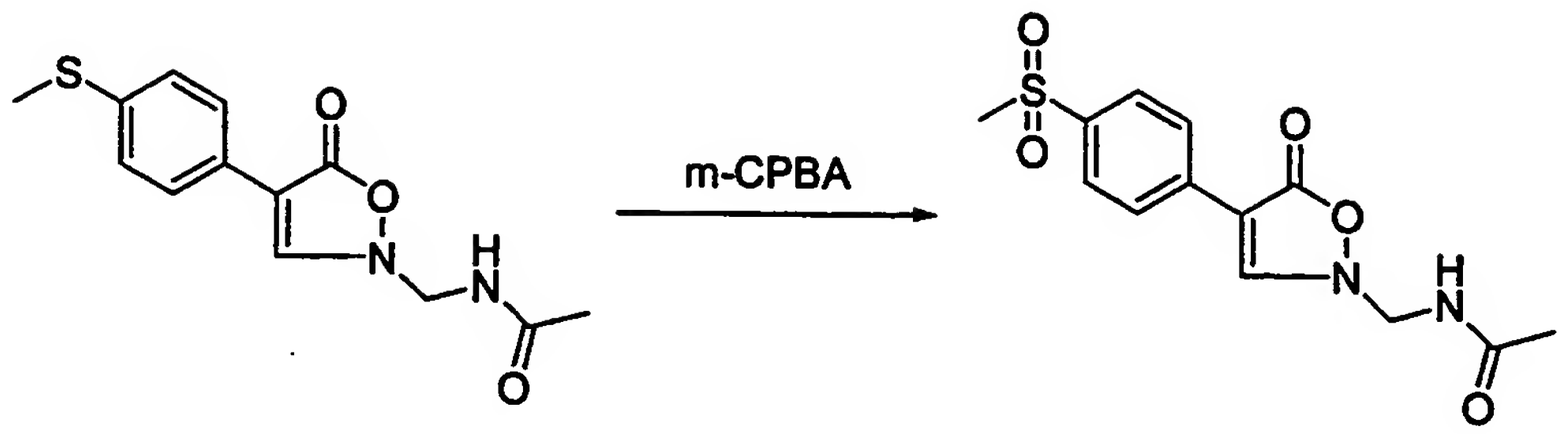
N-({4-[4-(methylsulfinyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide



To N-{[4-(4-methylthiophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (1.0 g, 3.6mmol) in 50 mL chloroform at 0°C was added m-CPBA (1.12 g, 3.6 mmol) in 30 mL chloroform via syringe pump over 2 hours. Saturated sodium bicarbonate was added and the reaction mixture was stirred vigorously for 10 minutes at which time it was poured into saturated sodium bicarbonate and 4:1 chloroform:methanol. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with ether providing 800 mg (79%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 9.11 (s, 1H), 8.96 (t, J = 6.1 Hz, 1H), 7.96 (d, J = 6.6 Hz, 2H), 7.67 (d, J = 6.6 Hz, 2H), 5.03 (d, J = 6.1 Hz, 2H), 2.73 (s, 3H), 1.84 (s, 3H); ESI $(M+H)^+$=295.

EXAMPLE 4

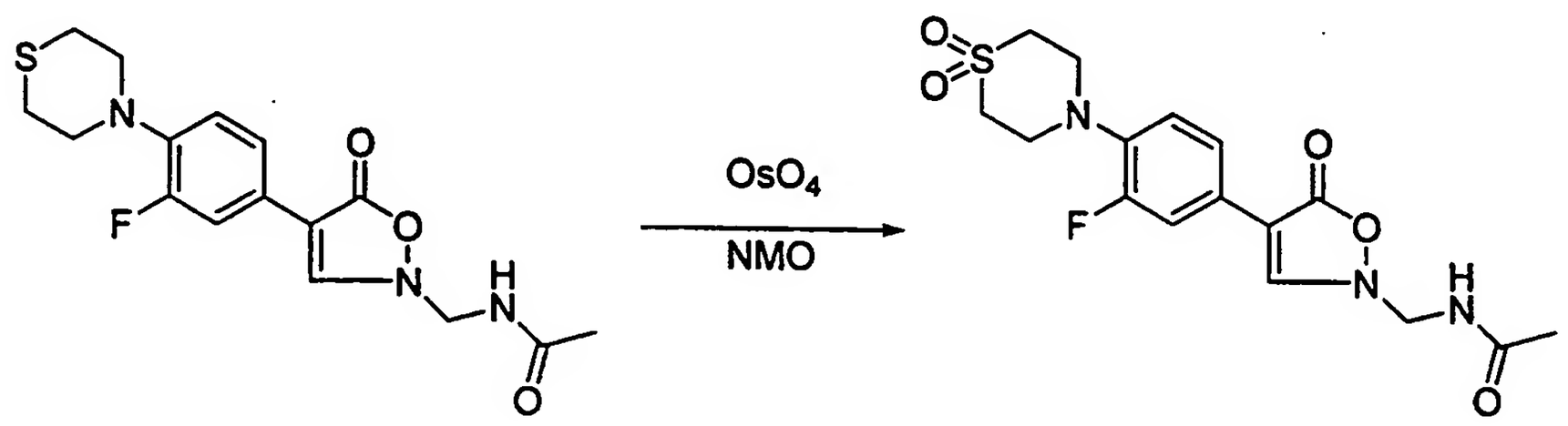
N-({4-[4-(methylsulfonyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide



To N-{[4-(4-methylthiophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (200 mg, 0.72 mmol) in 20 mL chloroform at 0°C was added m-CPBA (450 mg, 1.44 mmol) in 5 mL chloroform. After 30 minutes saturated sodium bicarbonate was added and the reaction mixture was extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was precipitated from acetone / 1:1 hexanes : ether providing 112 mg (50%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 9.24 (s, 1H), 9.01 (t, *J* = 6.1 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H), 5.11 (d, *J* = 6.2 Hz, 2H), 3.20 (s, 3H), 1.86 (s, 3H); ESI (M+H) $^+$=311.

EXAMPLE 5

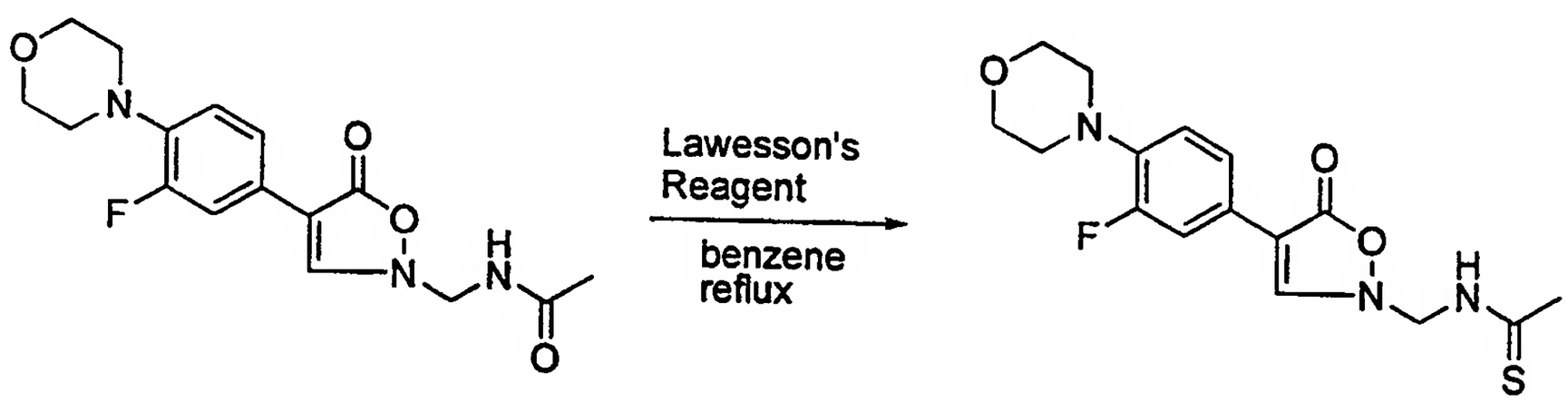
N-({4-[4-(1,1-dioxo(1,4-thiazaperhydroin-4-yl))-3-fluorophenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide



To N-{[4-(3-fluoro-4-(1,4-thiazaperhydroin-4-yl)phenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (100 mg, 0.29 mmol) in 2 mL water and 8 mL acetone was added N-methylmorpholine N-oxide (98 mg, 0.85 mmol) followed by osmium tetroxide (2.5 wt% in isopropanol; 7 μl; 0.07 mmol). After 18 hours at ambient temperature saturated sodium bisulfite was added and the reaction mixture was extracted with 4:1 chloroform:methanol. The organic layer was concentrated providing 85 mg (77%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 8.95 (s, 1H), 8.92 (t, *J* = 6.2 Hz, 1H), 7.62-7.51 (m, 2H), 7.17 (app t, *J* = 9.2 Hz, 1H), 4.99 (d, *J* = 6.2 Hz, 2H), 3.52-3.48 (m, 4H), 3.27-3.23 (m, 4H), 1.82 (s, 3H); ESI (M+H)$^+$=384.

EXAMPLE 6

4-(3-Fluoro-4-morpholin-4-ylphenyl)-2-{[(thioxoethyl)amino]methyl}-2-hydroisoxazol-5-one

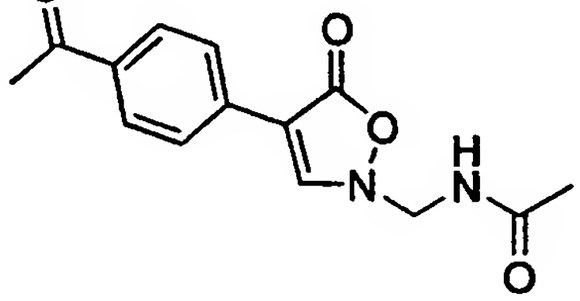


A mixture of N-{[4-3-fluoro-4-morpholinylphenyl-5-oxo-2-isoxazolinyl]methyl}acetamide (0.25 g, 0.75 mmol) and Lawesson's reagent (0.4 g, 1.0 mmol) in 10 mL of benzene was heated at reflux for 3 hours. The mixture was then concentrated under reduced pressure. The residue was purified using silica gel chromatography eluting with methylene chloride and ethyl acetate to give a colorless solid (80 mg, 30%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 1 H), 8.49 (s, 1 H), 7.50

(dd, J = 1.5 and 13.8 Hz, 1 H), 7.40 (dd, J = 1.5 and 10.2 Hz, 1 H), 7.12 (t, J = 10.2 Hz, 1 H), 5.56 (d, J = 6.3 Hz, 2 H), 3.94 (m, 4 H), 3.17 (m, 4 H), 2.57 (s, 3 H).

EXAMPLE 7

N-{[4-(4-acetylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide

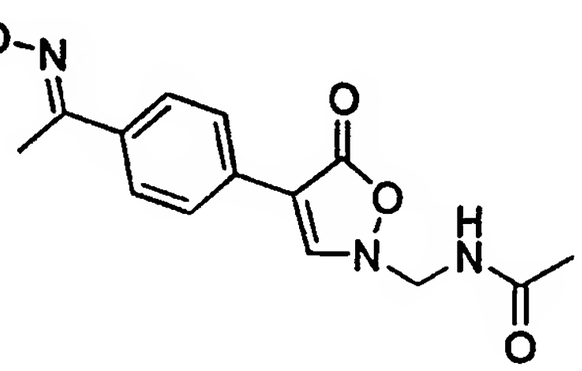


To N-{[4-phenyl-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (3.0 g, 12.9 mmol) and aluminum (III) chloride (13.8 g, 103.4 mmol) in 150 mL 1, 2-dichloroethane was added acetyl chloride (7.3 mL, 103.4 mmol) dropwise over 10 minutes. The resultant red mixture was heated to 80°C for 3.5 hours, cooled to ambient temperature, and poured over 10 minutes into a rapidly stirring mixture of 20% methanol/chloroform and 1N hydrochloric acid which was immersed in an ice bath. The mixture was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted twice with 20% methanol/chloroform, and the combined organics were then washed successively with 1N sodium hydroxide, saturated sodium bicarbonate, and brine. The organic layer was then dried over magnesium sulfate, filtered, and concentrated to an amorphous yellow solid which was dissolved in 20% methanol/chloroform. Ether was added and the mixture was stored at 0°C for 18 hours. The resultant precipitate was filtered to provide 2.48 g (70%) of the title compound as a pale pink solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 9.18 (s,

1H), 9.00 (t, *J* = 6.1 Hz, 1H), 7.96 (d, *J* = 6.7 Hz, 2H), 7.91 (d, *J* = 6.6 Hz, 2H), 5.10 (d, *J* = 6.2 Hz, 2H), 2.56 (s, 3H), 1.86 (s, 3H); ESI $(M+H)^+$=275.

EXAMPLE 8

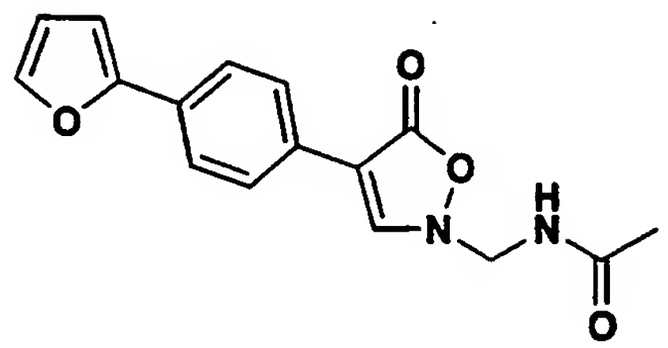
N-({4-[4-((hydroxyimino)ethyl)phenyl]-5-oxo-2-hydroisoxazol-2-yl}methyl)acetamide



A mixture of N-{[4-(4-acetylphenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (2.0 g, 7.3 mmol) and 50% aqueous hydroxylamine (1.0 mL, 14.6 mmol) was heated to reflux for 1.5 hours, concentrated to near dryness and redissolved in 20% methanol/chloroform. Hexanes were added until the solution became cloudy and the mixture was stored at 0°C for 3 hours. The precipitate was filtered providing 1.42 g (67%) of the title compound as a pale yellow solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 11.21 (s, 1H), 9.01 (s, 1H), 8.96 (t, *J* = 6.2 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 5.04 (d, *J* = 6.2 Hz, 2H), 2.19 (s, 3H), 1.84 (s, 3H); ESI $(M+H)^+$=290.

EXAMPLE 9

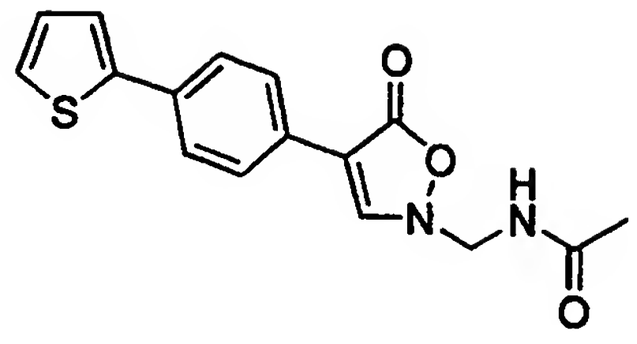
N-{[4-(4-(2-furyl)phenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide



Nitrogen was bubbled through a mixture of N-{[4-(4-iodophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (300 mg, 0.84 mmol), 2-tributylstannylfuran (0.26 mL, 0.84 mmol), tris(dibenzylideneacetone)dipalladium(0) (77 mg, 0.08 mmol), triphenylarsine (51 mg, 0.17 mmol), and lithium chloride (106 mg, 2.51 mmol) in 5 mL DMF. The reaction mixture was capped and allowed to stir at ambient temperature for 8 hours, at which time it was diluted with 20% methanol/chloroform, filtered thru celite and concentrated. The residue was suspended in chloroform, loaded onto a Biotage flash 40i chromatography module (12M) thru a frit, and eluted with 50% hexane/ethyl acetate providing a solid which was triturated with chloroform/ether to provide 132 mg (53%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 9.00 (s, 1H), 8.94 (t, J = 6.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.74-7.70 (m, 2H), 6.95 (d, J = 3.2 Hz, 1H), 6.60-6.59 (m, 1H), 5.04 (d, J = 6.1 Hz, 2H), 1.85 (s, 3H); ESI $(M+H)^+$=299.

EXAMPLE 10

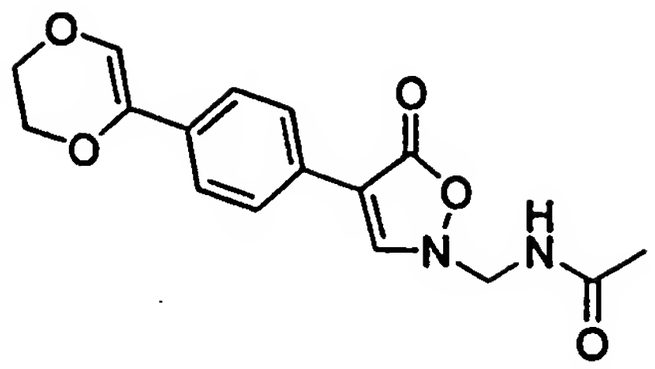
N-{[5-oxo-4-(4-(2-thienyl)phenyl)-2-hydroisoxazol-2-yl]methyl}acetamide



Nitrogen was bubbled through a mixture of N-{[4-(4-iodophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (300 mg, 0.84 mmol), 2-tributylstannylthiophene (0.27 mL, 0.84 mmol), tris(dibenzylideneacetone)dipalladium(0) (77 mg, 0.08 mmol), triphenylarsine (51 mg, 0.17 mmol), and lithium chloride (106 mg, 2.51 mmol) in 5 mL DMF. The reaction mixture was capped and allowed to stir at ambient temperature for 8 hours, at which time it was diluted with 20% methanol/chloroform, filtered thru celite and concentrated. The residue was suspended in chloroform, loaded onto a Biotage flash 40i chromatography module (12M) thru a frit, and eluted with 15% acetone/chloroform providing a solid which was triturated with chloroform/ether to provide 165 mg (63%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 9.00 (s, 1H), 8.95 (t, J = 6.0 Hz, 1H), 7.81 (d, J = 7.3 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.54-7.52 (m, 2H), 7.15-7.11 (m, 1H), 5.04 (d, J = 6.1 Hz, 2H), 1.85 (s, 3H); ESI $(M+H)^+$=315.

EXAMPLE 11

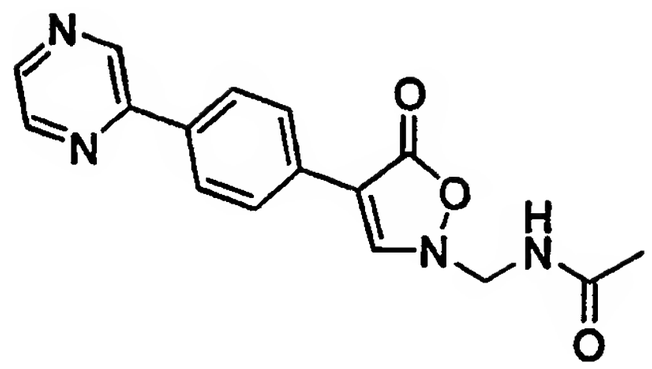
N-{[4-(4-(2H,3H-1,4-dioxin-5-yl)phenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide



Nitrogen was bubbled through a mixture of N-{[4-(4-iodophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (300 mg, 0.84 mmol), 2-(tributylstannyl)-5,6-dihydro-[1,4]-dioxin (346 mg, 0.92 mmol), tris(dibenzylideneacetone)dipalladium(0) (77 mg, 0.08 mmol), triphenylarsine (51 mg, 0.17 mmol), and lithium chloride (106 mg, 2.51 mmol) in 5 mL DMF. The reaction mixture was capped and allowed to stir at ambient temperature for 16 hours, at which time it was diluted with 20% methanol/chloroform, 10% aqueous potassium fluoride was added and the mixture was allowed to rapidly stir for 1 hours. The reaction mixture was filtered thru celite and concentrated. The resultant black oil was dissolved in 20% methanol/chloroform, adsorbed onto silica gel and loaded into a Biotage flash 40i chromatography module SIM. Chromatography was performed using a 12M silica gel cartridge eluting with 20% acetone/chloroform providing an amber oil which was triturated with ether, yielding 115 mg (44%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 8.93-8.88 (m, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 6.96 (s, 1H), 5.01 (d, J = 6.2 Hz, 2H), 4.22-4.19 (m, 2H), 4.10-4.07 (m, 2H), 1.85 (s, 3H); ESI $(M+H)^+$=317.

EXAMPLE 12

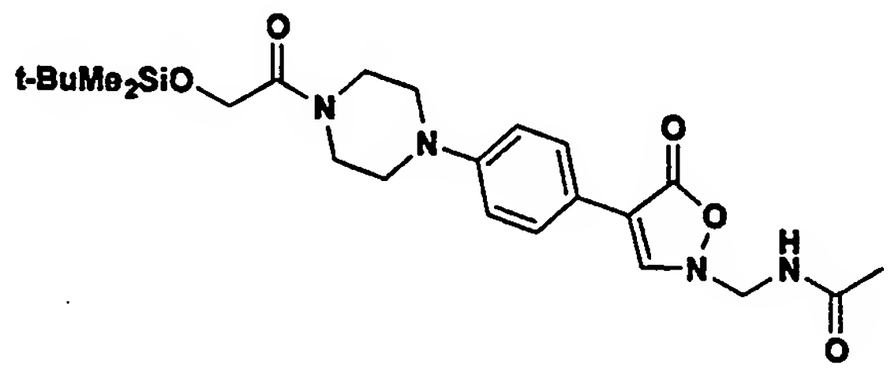
N-{[5-oxo-4-(4-pyrazin-2-ylphenyl)-2-hydroisoxazol-2-yl]methyl}acetamide



Nitrogen was bubbled through a mixture of N-{[4-(4-iodophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (300 mg, 0.84 mmol), 2-(tributylstannyl)pyrazine (340 mg, 0.92 mmol), tris(dibenzylideneacetone)dipalladium(0) (77 mg, 0.08 mmol), triphenylarsine (51 mg, 0.17 mmol), and lithium chloride (106 mg, 2.51 mmol) in 5 mL DMF. The reaction mixture was capped and allowed to stir at ambient temperature for 16 hours, at which time it was diluted with 20% methanol/chloroform, 10% aqueous potassium fluoride was added and the mixture was allowed to rapidly stir for 1 hour. The reaction mixture was filtered thru celite and concentrated. The resultant black oil was dissolved in 20% methanol/chloroform, adsorbed onto silica gel and loaded into a Biotage flash 40i chromatography module SIM. Chromatography was performed using a 12M silica gel cartridge eluting with 25% acetone/chloroform providing an amber oil which was triturated with ether, yielding 52 mg (44%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6; 300MHz) δ 9.28 (d, J = 1.4 Hz, 1H), 9.11 (s, 1H), 8.97 (t, J = 6.1 Hz, 2H), 8.71 (app t, J = 1.9 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H), 5.07 (d, J = 6.2 Hz, 2H), 1.86 (s, 3H); ESI $(M+H)^+$=311.

EXAMPLE 13

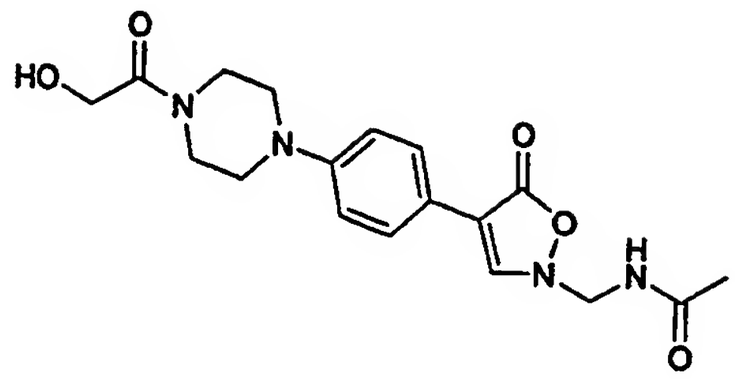
N-{[5-oxo-4-(4-{4-[2-(1,1,2,2-tetramethyl-1-silapropoxy)acetyl]piperazinyl}phenyl)-2-hydroisoxazol-2-yl]methyl}acetamide



To N-{[5-oxo-4-(piperazinylphenyl)-2-hydroisoxazol-2-yl]methyl} acetamide trifluoroacetate salt (0.43 g, 1.0 mmol) in 2 mL of dimethylformamide and 10 mL dichloromethane was added triethylamine (0.7 mL, 0.5 mmol) followed by (t-butyldimethylsilyloxy)acetyl chloride (1.0 g, 4.8 mmol). The resultant mixture was allowed to stir at ambient temperature for 1.5 hours before being partitioned between dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with ether to provide 0.24 g (49%) of the title compound. ^{1}H NMR (methanol-d_4; 300 MHz) δ 8.49 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 4.42 (s, 2H), 3.73 (t, *J* = 4.9 Hz, 4H), 3.24 (t, *J* = 4.9 Hz, 4H), 1.94 (s, 3H), 0.95 (s, 9H); ESI $(M+H)^+$ = 489.

EXAMPLE 14

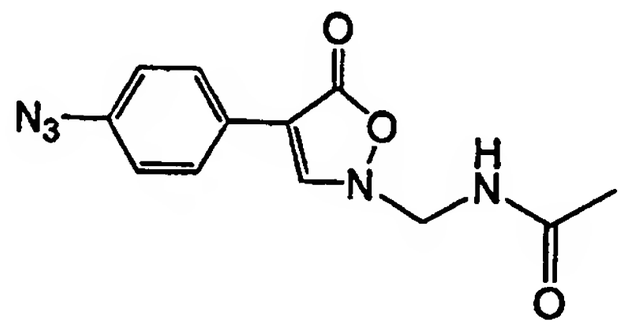
N-[(4-{4-[4-(2-hydroxyacetyl)piperazinyl]phenyl}-5-oxo-2-hydroisoxazol-2-yl)methyl]acetamide



To N-{[5-oxo-4-(4-{4-[2-(1,1,2,2-tetramethyl-1-silapropoxy)acetyl]piperazinyl}phenyl)-2-hydroisoxazol-2-yl]methyl}acetamide (0.3 g, 0.6 mmol) in 4mL dichloromethane was added 4 mL trifluoroacetic acid. After 1 hour, the reaction was concentrated, the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with ether to provide 92 mg (40%) of the title compound. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 8.87 (t, J = 6.2 Hz, 1H), 8.74 (s, 1H), 7.63 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 4.95 (d, J = 6.2 Hz, 2H), 4.64 (t, J = 5.6 Hz, 1H), 4.13 (d, J = 5.6 Hz, 2H), 3.60 (br s, 2H), 3.48 (br s, 2H), 3.17 (br s, 4H), 1.83 (s, 3H); ESI $(M+H)^+$=375.

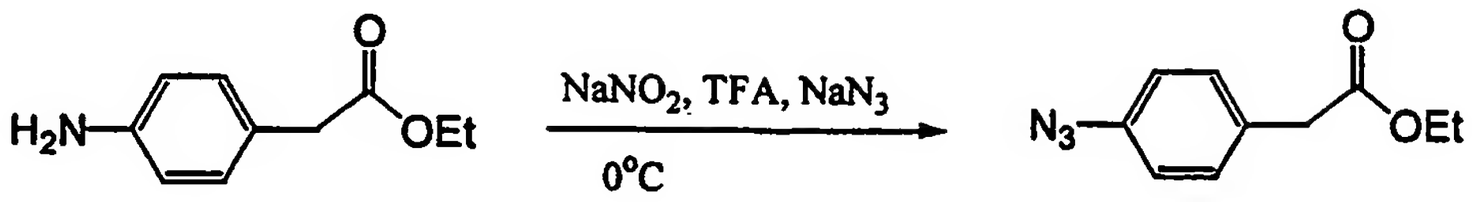
EXAMPLE 15

N-{[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide)



Prepared from ethyl 4-azidophenylacetate according to the general route outlined in Scheme 1. The starting material was prepared as follows:

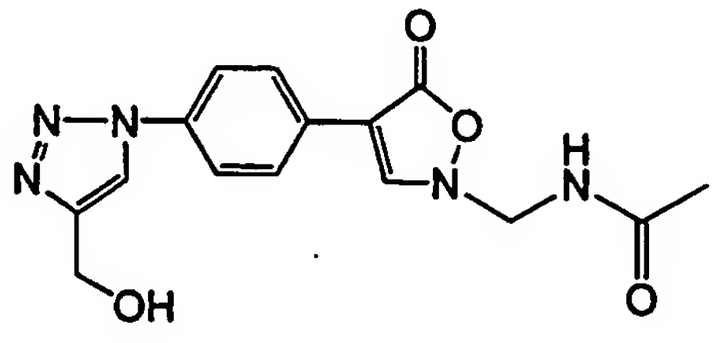
Ethyl 4-Azidophenylacetate



Following the general procedure of Marchesini (J. Org. Chem. **49,** p. 4287-4290, 1984), sodium nitrite (38 g, 0.56 mol) was slowly added to a stirred and cooled (0°C) mixture of ethyl 4-aminophenylacetate (25 g, 0.14 mol) in 700 mL of TFA. After the addition was complete, the reaction was stirred at 0°C for another 0.5 hour and then sodium azide (27 g, 0.42 mol) was slowly added over a period of 0.5 hours. The mixture was stirred for another 2 hours at 0°C and then quenched with ice water and the product was extracted with EtOAc. The organic phase was washed with water, dried over magnesium sulfate, filtered, concentrated to yield 26.5 g (90%) of the title compound as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.31 (d, J = 8 Hz, 2 H), 7.07 (d, J = 7 Hz, 2 H), 4.07 (q, J = 7 Hz, 2 H), 3.66 (s, 2 H), 1.17 (t, J = 7 Hz, 3 H).

EXAMPLE 16

N-[(4-{4-[4-(hydroxymethyl)(1,2,3-triazolyl)]phenyl}-5-oxo-2-hydroisoxazol-2-yl)methyl]acetamide

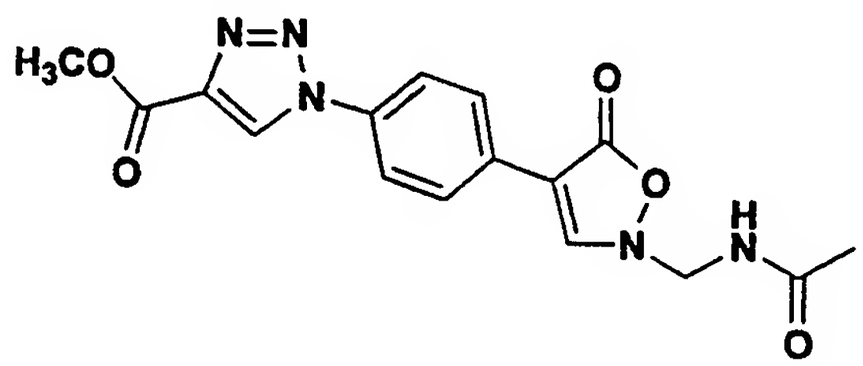


A mixture of N-{[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (80 mg, 0.29 mmol) and propargyl alcohol (0.1 mL,

1.71 mmol) in 3 mL of DMF was heated at 100°C for 10 hours. The reaction mixture was then concentrated in vacuo and purified by flash chromatography (silica gel; eluting with EtOAc followed by 10% MeOH/EtOAc) to yield 62 mg of a yellow solid. The ^{1}H NMR spectra indicated that the crude product was a mixture of two triazole isomers. These isomers were separated by preparative HPLC (H_2O/MeOH) to yield 10 mg (10%) of the title compound as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1 H), 8.96, (t, *J* = 6 Hz, 1 H), 8.69, (s, 1 H), 7.96 (m, 4 H), 5.07 (d, *J* = 6 Hz, 2 H), 4.61 (s, 2 H), 1.86 (s, 3 H).

EXAMPLE 17

Methyl 1-(4-{2-[(acetylamino)methyl]-5-oxo-2-hydroisoxazol-4-yl}phenyl)-1,2,3-triazole-4-carboxylate



A mixture of N-{[4-(4-azidophenyl)-5-oxo-2-hydroisoxazol-2-yl]methyl}acetamide (80 mg, 0.29 mmol) and methyl propionate (0.05 mL, 0.58 mmol) in 3 mL DMF was heated at 50°C for 24 hours. The reaction mixture was then concentrated in vacuo and triturated with EtOAc to yield 25 mg (24%) of the title compound as a yellow solid. (An alternate procedure which is more reliable involves conducting the reaction at room temperature for 10 days and then isolating as above.) ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.52 (s, 1 H), 9.15, (s, 1 H), 8.96, (t, *J* = 6 Hz, 1 H), 8.02 (s, 4 H), 5.08 (d, *J* = 6 Hz, 2 H), 3.90 (s, 3 H), 1.87 (s, 3 H).